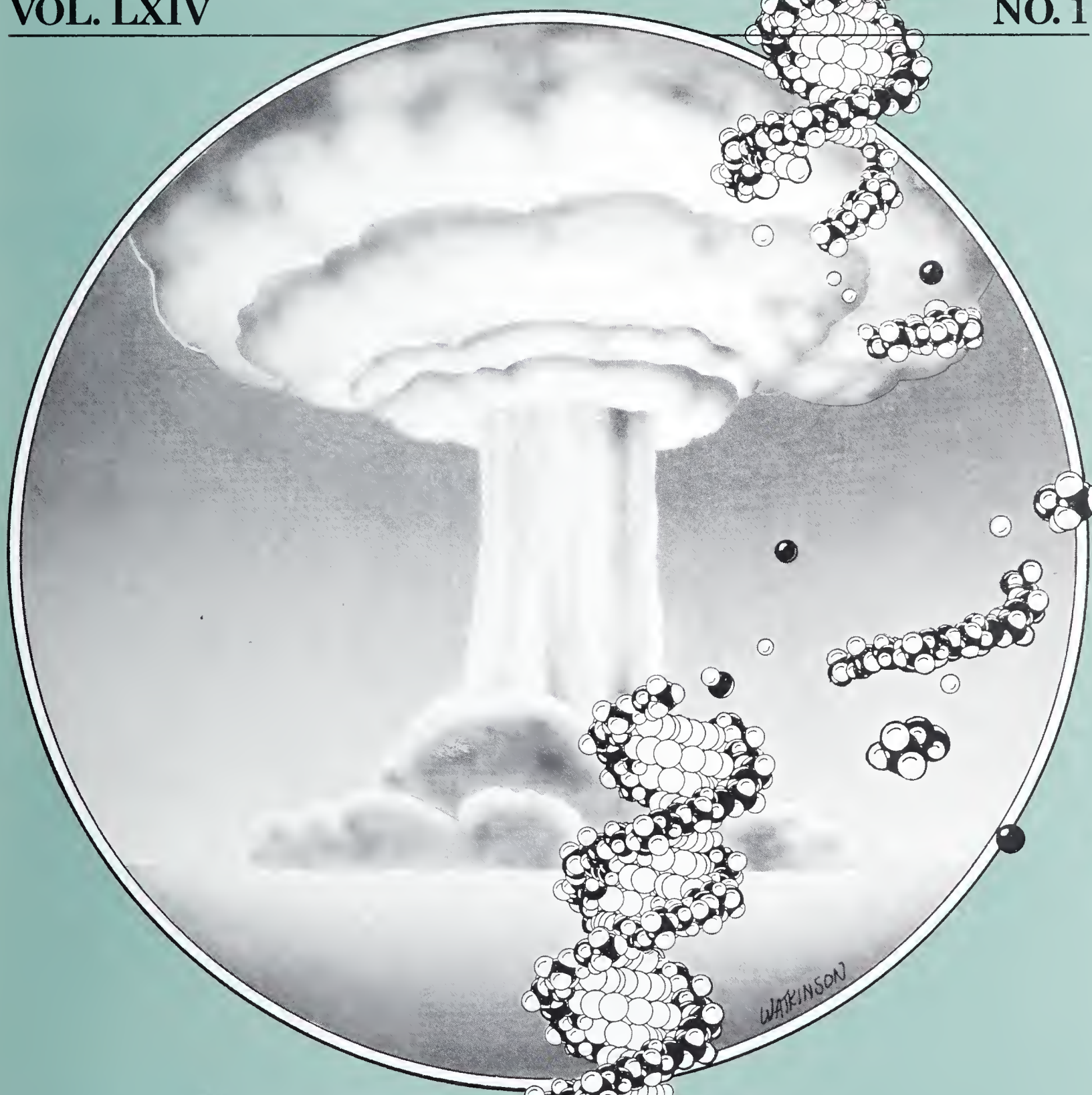
University of Toronto
MEDICAL JOURNAL
VOL. LXIV NO. 1



- REPORT FROM DEAN LOWY – THE CHERNOBYL DISASTER AND NUCLEAR WEAPONS
- CORONARY ANGIOPLASTY REVIEWED
- COMPUTERS AND MEDICINE

Digitized by the Internet Archive
in 2018 with funding from
University of Toronto

https://archive.org/details/medjournalDec1986uoft

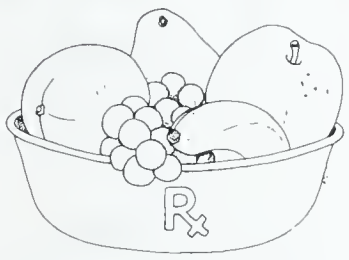
University of Toronto
MEDICAL JOURNAL

Established 1923. An Undergraduate Publication VOLUME 64, NUMBER 1 DECEMBER 1986

4 **Special Report** BY FREDERICK H. LOWY, M.D.
Report from Cologne – The Chernobyl Disaster and Nuclear Weapons

7 **Nutrition** BY MICHAEL PARÉ, B.Sc., M.Sc.
Diet and Cancer

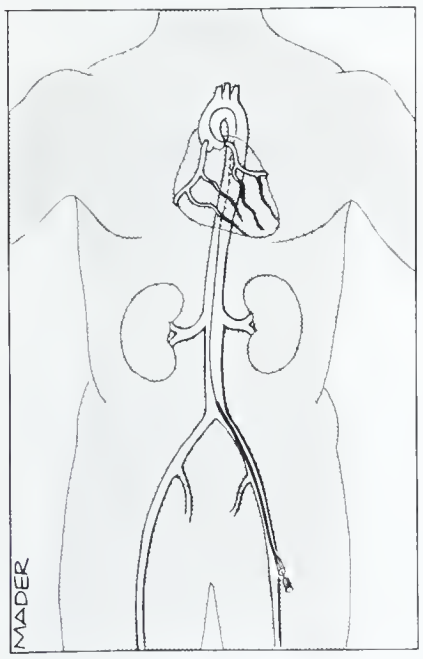
P. 4



12 **Cardiology** BY JAFNA L. COX, B.A.
Percutaneous Transluminal Coronary Angioplasty as a Current Therapy in the Treatment of Coronary Artery Disease

20 **Respirology Rounds – Question** BY CHARLES K. CHAN, ROBERT H. HYLAND, DONALD P. JONES and ROBIN R. GRAY
Poorly Resolving Pneumonia with Cavitation

P. 7



22 **Respirology Rounds – Answer**

24 **Cardiology** BY LLOYD C. SEMELHAGO, B.Sc.
The Effect of Propranolol and Epinephrine on Right Atrial Mechanical Function

28 **Orthopaedic** BY SHERIF P. NESSIM, B.Sc., ROBERT B. SALTER, M.D., F.R.C.S.(C), F.A.C.S.
Biomechanical Assessment of Joint Resurfacing: A Comparison of the Effects of Immobilization, Intermittent Active Motion and Continuous Passive Motion

P. 13

36 **Computers and Medicine** BY PETER WAN

40 **Book Reviews** BY JANIS M. MIYASAKI *et al.*

44 **Poetry and Short Stories**

P. 36

Cover: Illustration by Terry Watkinson AAM

Medical Alumni Association

• **THE MEDICAL ALUMNI ASSOCIATION** is the bridge between the graduates and the Faculty of Medicine, University of Toronto.

• The Association provides financial assistance (scholarships, bursaries, travel grants, fellowships loans) for undergraduates, as well as sponsoring programs that are of particular interest — General Practice Panel, Arts and Letters Committee, Undergraduate Affairs, Graduation Banquet, etc.

• At the Faculty level, there are two representatives on the Faculty Council, a representative on the Admissions Committee, and the Chairman of the Student Aid Committee is a representative on the Student Awards Committee.

• At the University level, the Association has two representatives on the Universtiy of Toronto Alumni Association, two representatives on the College of Electors, and a representative on the Varsity Fund Executive Committee.

• We are also represented on various Search Committees when Department Chairmen and the Dean of Medicine are being sought.

• The Association is also involved in providing some impetus to five year reunions. Two letters will be sent free of charge, for each class celebrating their reunion. Every attempt is made to keep an up-to-date address list of all our graduates. Please remember to notify YOUR Medical Alumni Association of any address change.

• The Association is governed by graduates who give their time and talent voluntarily. There is one full time employee. Donations given for Student Aid are used entirely for that purpose. Trust funds are administered, without charge, following the direction of the donor.

Editorial

This issue marks the 64th volume of the University of Toronto Medical Journal which was established in 1923. In this first issue of 1986-7, we have our feature article written by Dr. F.H. Lowy, Dean of the University of Toronto Medical School. The article focuses on a meeting of physicians discussing the issue of nuclear war. Although this is a medical journal, we feel it is our obligation as global citizens to occasionally spotlight issues that concern all of mankind. As members of a profession dedicated to serve the needs of people, it is our duty to become informed about nuclear issues, formulate an opinion, and most importantly, try to make this opinion understood. Hopefully, this article will stimulate some thought on the subject of nuclear arms.

In this issue, our Art directors Raymond Ng and Michael Pare have taken an exciting new approach in the artistic layout for the Journal. For instance, we introduced a new style for the content page by including some diagrams that appear in the later articles. These beautiful illustrations are the work of our germinating professional medical artists from the Department of Art as Applied to Medicine.

Also in this issue, we have a timely new section on Computers and Medicine introduced by Peter Wan. In future issues, the roles of computer in Clinical Medicine and Medical Research will be explored further.

With the help of Janis Miyasaki, we have also expanded our book review section considerably. In the last part of this issue, we have a new section devoted to poetry and short stories. The winners of the 1985-86 Arts & Letters Poetry and Prose contest are re-printed. The creation of a poetry and short story section will showcase the literary talents of medical students and allow the Journal reader to enjoy a contrast to the scientific articles presented. We hope this new section is both entertaining and stimulating.

In volume 63, number 2, March 1986, the Journal published an article entitled "The Spectrum of Stroke" by Steve West, Elizabeth Whittle, Robert Mounsey and Fred Parker. The article contained a detailed discussion of stroke and its pathogenesis. Dr. Michael L. Schwartz, year three neuroscience course co-ordinator and a neurosurgeon at Sunnybrook Medical Centre, devoted much time and effort into the production of this article. The article was edited by Dr. Schwartz and typed by his secretary, Sarah Pressman. However, due to a printer's error, they did not receive the acknowledgement they deserved. The authors of the article brought this to the Journal's attention and the Journal would like to take this opportunity to correct this error.

The staff of the Journal would like to thank all the subscribers, patrons, medical artists, and Journal volunteers for making this Journal possible. We wish that this issue will be enjoyable and informative to our readers.

Mahmood Kara
Robert Mounsey
Editors-in-Chief

Raymond Ng
Michael Pare
Associate Editors

Editorial Staff

Editors-in-Chief
Mahmood Kara, 8T8
Robert Mounsey, 8T8

Associate Editors
Raymond Ng, 8T8
Michael Pare, 8T8

Advertising Directors
Miah Hahn, 8T8
Nick Nianiaris, 8T8

Art Directors
Raymond Ng, 8T8
Michael Pare, 8T8

Editorial Board
Katie Birt, 8T9
Martin Boyer, 8T8
Jafna Cox, 8T8
Sarah Crowe, 8T8
Edsel Ing, 8T8
Nizar Mahomed, 8T8
Blake Papsin, 8T8
Shafiq Qaadri, 8T8
Anysia Rusak, 8T8
Lloyd Semelhago, 8T8

Book Review Editor
Janis Miyasaki, 8T8

Poetry and Short Story Editors
Scott Berry, 9T0
Ambrose Cheng, 8T8
John Kim, 8T9
Yvonne Opalinski, 9T0
Shera Vania, 8T9

Special Assignment Editor
Robert Loeb, 8T8

Computers In Medicine
Peter Wan, 8T8

Treasurer
Mustafa Rawji, 8T9

Art as Applied to Medicine
Vicki Earle B.Sc. AAM
Jackie Heda B.Sc. AAM
Stephen Mader AAM
Jane Wagner AAM
Terry Watkinson AAM
Mary-Anne Williams B.F.A./AAM

Secretary
Mrs. Audrey Randell

Report from Cologne – The Chernobyl Disaster and Nuclear Weapons

Frederick H. Lowy, M.D. *

The sixth International Congress of International Physicians for the Prevention of Nuclear War, which took place in Cologne in May and June, was overshadowed by the Chernobyl nuclear disaster. In his opening remarks, Dr. Bernard Lown of the Harvard School of Public Health, co-president of the association and, with Dr. Evgenyi Chazov of the Soviet Union, recipient of the 1986 Nobel Prize for Peace, pointed out that the accident at the Ukrainian nuclear power plant was yet another indication of the fallibility of the complex systems that we count on to prevent a nuclear war. He reminded a large, international audience that the Chernobyl tragedy, like the NASA Challenger failure, is directly attributable to a combination of human error and the failure of control systems. For the sake of our future on this planet, we must regard this as an ever present risk whenever we rely upon highly complex technology.

His point was clear to all present. That we have been disaster free for the forty one years since Hiroshima should not allow us to complacently depend upon superpower nuclear deterrence. The number of thermonuclear weapons with plutonium fission triggers in the arsenals of the United States and the Soviet Union is now estimated at 18,000. The potential destructive power of these weapons almost defies comprehension. Each of these, thousands of times more powerful than the 13 kiloton bomb that devastated Hiroshima, is sufficient to obliterate a city of more than 100,000 people. The irony of the situation is that there are only about 3,000 cities of this size in the world to serve as targets for these 18,000 weapons. A single modern nuclear submarine, like the US Trident, with its 24 MIRVed missiles with 240 nuclear warheads of 100 kilotons each has eight times the potential firepower of all the armies that fought in World War II.

Since the 1950's when the US monopoly on nuclear weapons was broken, the world's superpowers have relied on a policy of deterrence to guard against nuclear attack. The knowledge that a first strike would not prevent massive retaliation has given the Soviet Union, the United States, and their allies a measure of comfort in the realization that no sane leader in either Moscow or Washington would risk national suicide by attempting to 'win' a nuclear war.

The comfort level has dropped considerably during the past couple of years as military leaders and, surprisingly, some political leaders too have spoken of "limited" or "tactical" nuclear wars and the possibility of significant parts of the population surviving such an event. Whether any nuclear attack, however limited its intent, can be contained is highly doubtful given the short reaction times available to "the other side". And to argue that any nation, including even countries in the southern hemisphere, can escape massive devastation is hardly possible in the light of what is known today about the immediate and long term effects of multiple nuclear explosions.

Certainly, the International Physicians for the Prevention of Nuclear War have persuasively demonstrated that there is no effective medical response to such a disaster. That is, perhaps, the major message that this organization has delivered. Only six years old, the organization now has a membership of 140,000 physicians in over 40 countries. They have reminded us that in the event of nuclear catastrophe most physicians and hospitals, located as they are in large cities, would be obliterated. Those health professionals remaining alive and functioning, with limited medical supplies, would be ridiculously inadequate to care for thousands of severely injured pain wracked survivors.

It is for this message, and its remarkable influence in establishing meaningful east-west dialogue on this issue, that IPPNW was awarded the Nobel Peace Prize this past year. Dr. Lown and his co-president, Soviet cardiologist, Dr. Evgenyi Chazov, accepted the Nobel Prize in Peace on December 11, 1985, in Oslo.

The point made by Dr. Lown in Cologne was that, quite apart from the danger of false thinking about the capacity to "win" a nuclear war by utilizing a first strike strategy, the superpowers and the world are at risk simply because there are so many nuclear weapons available. Further, the weapons are widely dispersed and an increasing number of military personnel have critical access to them. Of course, in addition to the United States and the

Logo for International Physicians for the Prevention of Nuclear War

* *Dean, Faculty of Medicine, University of Toronto*

Soviet Union, it is known that Britain, France, and China also have nuclear weapons at the ready and it is highly likely that India, Israel, Pakistan, and South Africa do as well. Other countries can be expected to follow or have already done so. In all of these countries, fallible human beings are manning fallible complex weapon systems. Fallible US and Soviet early warning systems attempt to distinguish genuine nuclear attacks from false alarms due to an incredibly large number of potential causes.

This is the point that Dr. Lown made with respect to the US Challenger failure and the Soviet Chernobyl nuclear accident. In each instance, great care had been taken to achieve safety yet the inevitable failure of high technology, created and operated by fallible persons, led to disaster. Given the multiplicity and complexity of nuclear weapons systems, a catastrophic breakdown becomes a frightening statistical probability.

The Chernobyl accident of course influenced the IPPNW delegates more directly than through Dr. Lown's words. Germans and other central Europeans subject to radioactive fallout had received a grim reminder that radiation knows no national boundaries. And Soviet physicians, who participated prominently in the conference, were unusually frank and forthcoming about the unhappy medical consequences of the Chernobyl disaster. At the time of the conference, from May 28 to June 1st, Dr. Chazov and his colleagues revealed that 25 people had already died, mostly from radiation poisoning. Dr. Yuri Lopukhin, a senior hospital director in Moscow, spoke to me sadly about the failure of currently available procedures, including bone marrow and fetal liver transplants, to save the lives of victims inadvertently exposed or of firemen who were poisoned while fighting the initial Chernobyl explosion. While grateful to physicians and others in Western countries who provided or offered assistance, the Soviet delegates expressed great concern that their Western colleagues did not seem to appreciate fully the significance of the nuclear power plant accident in relation to the incomparably more dangerous risks posed by nuclear weapons.

In fact, attending such a conference for the first time (together with some 40 other Canadian physicians and students) I had no doubt about the seriousness with which the nuclear threat was taken by our European colleagues. This is in contrast to the attitude of the majority of North American physicians. Although Physicians for Social Responsibility (in the United States and the Canadian Physicians for the Prevention of Nuclear War) are growing in membership, most physicians and an even greater proportion of citizens, generally turn a blind eye to the nuclear risk.

During the Cologne Congress I learned from Dr. John Dawson of the British Medical Association that physicians in the United Kingdom are increasingly taking note of their potential for influencing public opinion and government in this matter. Two BMA publications 'The Medical Effects of Nuclear War' (John Wiley and Sons) and the recently published 'The Long Term Environmental and Medical Effects of Nuclear War' (BMA House) have been very well received by UK physicians. The Cologne IPPNW Congress was reported by the major British papers. The German press gave close coverage to the Con-

Logo for Science of Peace

gress, focusing largely on the Chernobyl-nuclear war connection, the risk from German nuclear plants and the participation of major German political figures, especially Johannes Rau, Premier of North Rhine-Westphalia and the socialist candidate for the chancellorship of West Germany. Other international figures prominent at the Congress were: David Lange, Prime Minister of New Zealand, who gave the keynote address; John Kenneth Galbraith of the United States; and Inga Thorsson of Sweden.

The beautiful city of Cologne on the Rhine River served as an appropriate backdrop for the IPPNW Congress. Although it has been completely rebuilt after World War II and many of its medieval structures restored or duplicated, the city contains many indicators of modern Germany's turbulent history. An exhibit of the devastation caused by Allied bombing in World War II was closely positioned near vivid mementos of the ravages of Germany's Nazi regime.

A most moving and solemn experience for the physician delegates was a ceremony at Cologne's extensive cemetery complex. Many of Cologne's 13,000 civilian victims of World War II air aids are interred together, two to a grave. Other sections contain graves of thousands of forced laborers who met miserable deaths in Germany where they were brought as forced laborers from all over occupied Europe. There are other grim reminders of the Nazi era: mass graves for victims of Gestapo torture; Germans who were exterminated, with the consent and assistance of physicians, because they were mental patients, epileptic, physically handicapped or members of "inferior races", and were considered "unworthy of life"; and a Jewish cemetery containing the remains of some of Cologne's 11,000 Jews who were put to death, the majority in extermination camps further east. As the hundreds of German and visiting physicians and the German churchmen who addressed us walked slowly through the vast cemeteries, carrying flowers or lit candles, the evidence of man's inhumanity to man was palpable.

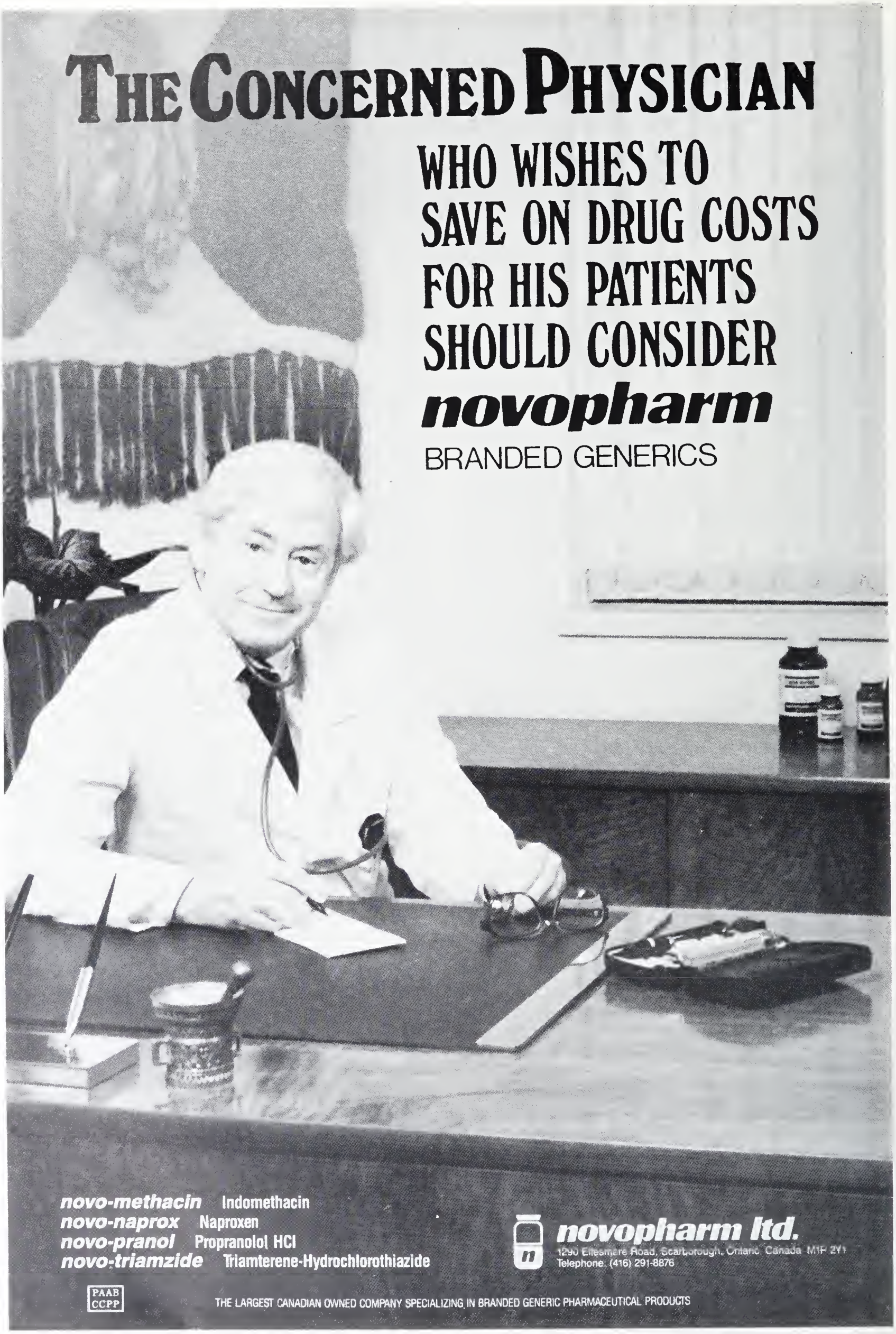
The physicians' anti-nuclear war movement, which finds its most public expression in those international IPPNW congresses, arose from the belief that we, as knowledgeable professionals, have a duty to warn our fellow citizens that a nuclear holocaust would threaten the very existence of life on this planet. The Chernobyl nuclear accident and the Cologne cemetery both served to underscore this message.

THE CONCERNED PHYSICIAN

WHO WISHES TO SAVE ON DRUG COSTS FOR HIS PATIENTS SHOULD CONSIDER

novopharm

BRANDED GENERICS



novo-methacin Indomethacin
novo-naprox Naproxen
novo-pranol Propranolol HCl
novo-triamzide Triamterene-Hydrochlorothiazide

novopharm ltd.
1290 Ellesmere Road, Scarborough, Ontario Canada M1P 2Y1
Telephone: (416) 291-8876

PAAB
CCPP

THE LARGEST CANADIAN OWNED COMPANY SPECIALIZING IN BRANDED GENERIC PHARMACEUTICAL PRODUCTS

Diet and Cancer

Michael Paré, B.Sc., M.Sc., 8T8

Diet and nutrition are areas of science in which laymen think they are the experts and claim to know just what is "good" to eat and just what is "bad" to eat — while the real experts (the nutritionists, biochemists and epidemiologists) ironically claim no such knowledge, except in very modest and qualified terms. Both sides have contributed to this confusing reversal of roles. Members of the general public overestimate their understanding of diet and nutrition (D & N) because of their ignorance of the scientific method and because of their overestimation of the importance of anecdotal evidence. Medical scientists have generally underestimated the importance of diet and nutrition with their assumption that D & N (except in severe malnutrition) does not really have any important impact on human health[9]. Nutrition, it has been said, is a subject "somewhat foreign to the medical mind"[9]. Fortunately this situation is now rapidly changing and the relationship between D & N and health and disease is now receiving the scientific attention it deserves by the medical establishment.

On the top of the list of diseases linked to D & N is that most dreaded of them all: CANCER. There is some good news and some bad news. The good news first: there is a growing body of evidence that components of our diets may actually inhibit the molecular chain reactions that lead to the initiation and promotion of cancer cells. The bad news dampens our mood somewhat when we learn that many components of our diets contain a great variety of natural and "additive" mutagens and carcinogens. The National Research Council (USA) has recently published an in-depth committee review, by several leading scientists, of the available scientific evidence relating Diet & Nutrition to Cancer[1].

The Epidemiology of Diet and Cancer

Recent interest in the relationship between D & N and cancer has been enhanced by studies in which large differences in cancer incidence and type of cancer have been found between different countries. This cannot be explained by genetic differences secondary to ethnic origin since when people migrate from one country to another they tend to acquire the cancer incidence rates characteristic of their new location rather than retaining the cancer incidence rates of their native lands. This strongly suggests an environmental causation. That environmental factors are a cause of some cancer is fairly obvious and has been known for a long time[2]. This was first shown by the English surgeon Sir Percival Pott, who noticed the unusually high incidence of scrotal cancer among chimney sweepers which was due to contact with compounds in soot[7]. More recently epidemiologists have shown an association between cigarette smoking and lung cancer. It is now thought that as many as one-third of all cancer deaths in the United States are caused by tobacco. In addition the chemical products and by-products of industralization (both useful compounds and pollutants) have been increasing under suspicion as possible carcinogens. The popular press fuels these suspicions by painting a terrifying picture of our ecosystems being quickly destroyed by massive contamination by industrial chemical carcinogens. This is simply not true, according to epidemiological studies. Although the number of people dying of cancer has indeed increased this is primarily due to: A) The cancer caused by tobacco (smoking and chewing)[3] and B) The increasing life expectancy[1]. As people live longer there is an increase in the incidence of cancer because cancer is an old peoples' disease. In fact, when adjusted for age the incidence of those cancers not associated with smoking have actually declined since

World War II[9]. Of course, this does not rule out the possible future causes of cancer being linked to industrialization and any new chemical products. Thus we must continue to be on guard against this possibility[7].

Fat: It has been relatively easy to demonstrate an association between the diet consumed in our modern affluent North American society and the incidence of breast, colon and uterus cancers[1]. For example there is a high correlation between the total per capita fat intake and the national rate of breast cancer mortality among women ($r = 0.89$), and colon cancer in both women ($r = 0.81$) and men ($r = 0.85$)[4]. Of course, the amount of fat in the diet is not the only difference that distinguishes the diets of low-fat and high-fat consuming populations in different countries. Therefore it has proven to be quite diffi-

cult to establish causal relationships and to determine which of the specific dietary components are the responsible cancer causing agents[1]. The problems of precisely analyzing diet are several fold[4]:

1) Diet is subject to considerable individual variation.
2) Foods are extremely complex substances and are getting even more complex with our increasing reliance on processed foods.
3) Memory of foods consumed is of variable reliability.
4) Even in "natural" food-products such as fruits and vegetables there is considerable variation in some dietary elements depending on where the food was grown.

Nevertheless a number of useful methods for assessing dietary intake have been developed. These include questionnaires determining the usual frequency of consumption of various foods, food diaries and interviews about previous dietary intake[4]. Another method is an analysis of food produced in a country as well as the amount exported, imported, fed to livestock, lost in storage, etc. For other foods, analysis of biologic specimens can substitute for information on dietary intake. Serum levels of carotene and vitamin E are sensitive to dietary intake and can therefore be used to study the relationship of these nutrients with cancer[4].

To get a clearer idea of how diet effects cancer incidence, and to disentangle environmental causality from genetic predisposition, it is useful to study people who have radically changed the composition of their diet. It was found that for populations that had migrated from one country to another — and had thus adopted the diet of the new country — that their pattern of cancer was intermediate between the old country and the new[7]. After one or more generations, migrants acquired the cancers characteristic of the host country. For example, the Japanese who migrated to the U.S. in the early twentieth century had a very low mortality rate for breast cancer as compared to the general population of the USA. The mortality rate climbed for the 2nd generation and by the 3rd generation was almost equal to that of the native population. This was not due to inter-marriage with the general population since this was at a very low level[1]. These studies do not, of course, prove that diet was the cause of the change in cancer pattern but certainly are consistent with this possibility. Further studies have supported this interpretation.

Some religious groups follow diets that differ from the general population and so can be examined to see if this effects cancer incidence. For example Seventh Day Adventists, who abstain from tobacco and alcohol and are vegetarians, have a lower rate of colon cancer than did a comparable control group. (See below for importance of control group). In Bombay India, the Hindu community, a religious group that follows a strict vegetarian diet, has a much lower level of cancer of the breast, and colon than do the Parsi Bombay community who eat a more Western-style diet[1]. Of course, there are many differences other than dietary factors between different religious groups and so the above evidence should be interpreted as a possible dietary effect. Sir Richard Doll of Oxford, a leading cancer epidemiologist of the Imperial Cancer Research Fund, has published major studies correlating environmental factors including diet with cancer. These massive descriptive studies again implicate several dietary components. Doll et al. found that there was a correlation between meat and fat intake and cancers of the colon and rectum, breast, uterus and ovary[4]. Additionally there is a higher rate of testicular and kidney cancer in high fat eaters, an increase in intestinal cancer with increase in sugar consumption, an increase in pancreatic cancer with high egg consumption, and lower cervical cancer rates with higher fruit consumption[4]. Although they are very useful, the above studies lack certain advantages of case-control studies. This kind of study, enable investigators to collect data for individuals rather than for groups and they are thus designed to control for confounding variables[1]. For example — dietary intake is collected for cases with a specific type of cancer and are then compared with similar exposure data for a suitably selected non-cancer "control" group. If done properly differences in exposures related to variation in cancer incidence may actually reflect a causal relationship. Anthony B. Miller and colleagues, of the University of Toronto, conducted such a case-control study on 400 breast cancer cases and 400 controls. They found the strongest correlation with total fat consumption[1,4,7]. And they also found a dose-response, curve between amount of saturated fat eaten and breast cancer. This is particularly important since it points to a possibility of reducing cancer risk by reducing fat intake. Although there is still some controversy over just how important fat is to the development of breast cancer the Committee on Diet, Nutrition and Cancer stress that "Both the high incidence of and mortality from breast cancer have been shown to correlate strongly with high per capita fat intake; the few case control studies conducted have also shown this association with dietary fat"[1].

The results from a substantial number of epidemiological case-control studies have also indicated an association between dietary fat and cancers of the gastrointestinal tract[1,5]. The association appears to be particularly strong for saturated fat. However other studies of fat intake have failed to find any significant association. Nevertheless other laboratory evidence (see later) strengthens the association between fat intake and cancer and so this finding should be taken quite seriously.

Fiber: The good news here is that dietary fiber in the form of grains and vegetables may have a protective effect against colon and rectal cancers[2,5]. Interest in this area was largely the result of work by Dr. Denis Burkitt in Africa[2]. He observed that there were low rates of colon cancer in areas where fiber consumption and stool bulk were high. He proposed that a high fiber diet was protective. Although on the surface this seems like a simple and straightforward theory — it is not. Some studies have interpreted the seemingly protective effect of fiber as illusionary. It is thought to be due to confounding variables since there are many other dietary differences between high-fiber consumers and low fiber consumers. It has been suggested that the inverse relationship between fiber intake and incidence of colon cancer is secondary to higher cholesterol consumption in high incidence nations. In addition although most studies do find this

association of high fiber/low-colon cancer, just what the protective dietary element is, is not so clear. High fiber diets can be those with lots of fruits and vegetables which are also major sources of several vitamins and other compounds that have been shown to be anti-carcinogens[3]. Some of the inconsistency in findings about fiber is undoubtly related to the extremely heterogeneous nature of "crude fiber" which is the term usually used by nutritionists. More recent data suggest it may not be "fiber" per se but rather a specific fiber component: the pentosan fraction that may be important[4].

Nevertheless it has been concluded that "Although the available epidemiologic data are not entirely consistent, the weight of evidence generally supports the hypothesis that fiber protects against colon cancer"[1].

Vegetables: Evidence is growing that your mother was even more right, than even she thought, when she urged you to eat all your vegetables because they were good for you[3]. A number of studies suggest a protective role against colon and rectal cancers — for cruciferous vegetables — cabbage, broccoli, cauliflower and brussels sprouts. In addition further research has found that other kinds of vegetables including lettuce and carotene rich vegetables are related to lower rates of stomach cancer[1,7].

Minerals and Vitamins: Although it has been widely known for sometime that certain minerals and vitamins have profound effects on the health of people under normal conditions it has more recently come to light that other minerals (for example Selenium) have similarly important health effects related to cancer in humans[1,6]. Selenium, a naturally occurring trace element, has been reported as having a protective effect against cancer, especially of the gastrointestinal and genitourinary tracts. One study compared the blood selenium levels in cancer and normal subjects and found that patients with gastrointestinal cancers and Hodgkin's disease had significantly lower levels. Mexico has a lung cancer death rate one-ninth that of the USA. Mexican smokers consume about three-quarters the number of cigarettes that the typical American smoker consumes — but this by itself cannot explain the large difference in mortality rate. Although there is no significant difference in the amount of tobacco tars and nicotine between Mexican and American cigarettes there is a big difference in the content of Selenium. The Mexican cigarettes contain three times the level of Selenium that the American cigarettes have[6].

The scientific evidence outlined above — although vague and conflicting in some respects (in a large part due, no doubt, to the extremely complex nature of epidemiological research) — clearly establishes an important link between D & N and cancer. To get a better handle on the problem and to move from studying associations to studying causal relationships prospective-cohort studies should be undertaken. A prospective cohort study (PCS) is the silver standard of epidemiological research[1]. It focuses on individuals and therefore controls for confounding variables. Furthermore PCS are less susceptible to bias than are case control studies because the exposure data are collected prior to the occurrence of the disease. In PCS, occurrence rates of disease over time are compared between groups of individuals with similar characteristics but with different levels of exposure to the factors being studied. Unfortunately because the low incidence of the disease requires following large groups over extended time periods, these studies are expensive and very time consuming. In addition PCS suffer a limitation because cohorts are self-selected rather than being randomly assigned. Therefore the true gold standard, because it is the most scientifically rigorous approach, is the intervention study, also call the randomized trial[1]. In these studies the investigators randomly assign (optimally in a double blind fashion) — the subjects to two (or more) groups, which are then exposed or not exposed to different levels of the substance being studied. As useful as this type of study is scientifically, it must be stressed that experiments using human beings are justifiable only after considerable experimental and epidemiological data have been amassed to ensure that a beneficial result is at least likely and that an adverse effect very unlikely. In relation to D & N and cancer this criterion has been fulfilled and so this kind of study has recently begun[6]. In Seattle, Washington a "Cancer Prevention Research Unit", of the University of Washington School of Public and Community Medicine, was opened in 1984. It has been conducting massive new studies aimed at seeking means of preventing the leading cancers. The Seattle program is focusing mainly on ways to prevent lung cancer with putative anti-carcinogens. These anti-cancer chemicals will be tested for their effectiveness on 15,000 heavy smokers and also 2,500 shipyard workers who have had at least 20 years exposure to asbestos, a powerful carcinogen[6]. These putative anti-carcinogenic compounds are discussed in more detail in the following section.

Laboratory Methods and Findings

As interest in the possible relationship between diet and cancer has grown in recent years, increasing attention has been paid to the chemical carcinogens in our diet. The

foods that we eat contain an extraordinary number and variety of chemical constituents[3]. It is estimated that there may be as many as 3000 substances intentionally added to foods during processing, another 12,000 usually from packaging materials (classified as unintentional additives) and countless others in greater numbers than these as the natural components. Most of these chemicals are present in relatively low concentration, but even very small amounts of potent carcinogens (e.g. aflatoxin) can potentially exert deadly effects. In the laboratory, investigators have attempted to elucidate the mechanisms by which dietary components influence carcinogensis. They have tested the ability of particular diets, individual nutrients, food extracts, and non-nutrient dietary components of food to enhance or inhibit the development of cancer. Alternatively they have determined a chemical's ability to cause mutation as a measure of its carcinogenic potential. Often the diets or compounds tested have been suggested by epidemiological studies, which point to them as potential culprits. In fact, it is this gathering support from several different avenues of research, which tend to reinforce each other, that has provided the most convincing evidence for implicating certain dietary components.

Fat: There is considerable laboratory support for a role of fat in the genesis of cancer. Increasing the level of dietary fat from 5% to 20% of total calories in mice increases the incidence of some chemically induced breast-cancer tumors. Fat also increases the growth of transplantable adenocarcinoma tumors. In addition, animals that have a low fat diet have a lower breast tumor incidence. Similar results have been obtained for colon cancer: A higher dietary quantity of fat ($\approx$20%) increases or potentiates the carcinogenic effect of various compounds. It has been suggested by Bruce Ames, a leading cancer biochemist, that when fats are metabolized in the body they trigger a destructive chain reaction known as lipid peroxidation, which yields a variety of oxygen radicals which may explain their carcinogenic effect[3]. Because of their potent chemical reactivity, these high energy forms of oxygen can cause widespread damage within the cell. They interfere with DNA, cross linking it with other molecules of DNA, or to protein, and generally disrupt numerous cellular functions and structures. In light of the combined epidemiological and experimental evidence the committee on Diet, Nutrition and Cancer concludes that: ". . . of all dietary components . . . studied the . . . evidence is *most* suggestive for a causal relationship between fat intake and the occurrence of cancer"[1].

Fiber: Similar laboratory support for the epidemiological evidence in the case for dietary fiber's protective role in colon cancer is not as abundant. Although a few experimental studies have shown that some types of high fiber ingredients (e.g. cellulose and bran) reduce the tumorigenicity of certain chemical carcinogens. There is a distinct lack of experimental results. As the Diet, Nutrition and Cancer Committee conclude "Further information is needed on the basic chemistry and biological effects of fiber and its components to pursue experimental studies that will produce meaningful results"[1].

Vegetables and Fruits: Much more impressive is the supporting evidence for certain vegetables and fruits as being protective against cancer. Several vitamins are known or suspected of being anti-carcinogens. Vitamin A, its precursor carotenoids, and its synthetic analogue retinoids, decrease susceptibility to carcinogenesis in some animals to some types of cancers. In addition, a deficiency in Vitamin A generally lowers the threshold level of some carcinogens to produce tumors in laboratory animals. Interestingly it has been found that carotenoids may protect against oxidative reactions by quenching free radical oxygen and thus limiting damage to DNA[1,3,7].

Although the case for Vitamin C and Vitamin E is not as strong as for Vitamin A there is considerable theoretical evidence to explore such possibilities further. Therefore, although the epidemiological evidence is not strong, the laboratory studies make an anti-carcinogenic role a logical possibility. In laboratory tests vitamin C can inhibit the formation of carcinogenic N-nitroso-Compounds. It is also known to be an anti-oxidant which is particularly interesting in so far as many known anti-carcinogens are antioxidants. There are also data that suggest vitamin C may actually stimulate growth of certain tumors in some experimental situations. Vitamin E (tocopherol) also inhibits the formation of N-nitroso-compounds. It seems to act as a free radical scavenger and has been found not only to protect against radiation-induced DNA damage but also chemically induced carcinogenesis[1].

It must be noted that there are many other components of vegetables which are potential anti-carcinogens. For example glutathione is present in food and is one of the major antioxidants and antimutagens in the soluble fraction of cells[3]. Other compounds present are aromatic isothiocyanates, indoles and phenols. These have been found to inhibit chemically induced carcinogenesis in laboratory animals[3]. Although these findings are encouraging it should not be interpreted that just because these compounds have these effects in animals that they indicate that humans should start to consume them in large amounts. Indeed they may have adverse health effects on people. Clearly more information is needed in this area[6].

Selenium: The evidence backing the case for selenium is also quite impressive[4]. It has an important role in the activity of glutathione peroxidase an enzyme that protects against oxidative tissue damage at a cellular level. A large number of *in vitro* studies and studies using animals support the hypothesis that increased intake of selenium reduces the risk of cancer in humans. Selenium decreases the mutagenic activity of a variety of well known carcinogens in the Ames mutagenicity assay. It has been found to be protective against tumor production by a number of carcinogens. It is thought that its possible mode of action is to act as an antioxidant agent. This is consistent with evolving theories which link many carcinogens to the production of free oxygen radicals.

Micronutrients: There is increasing evidence that along with potential macronutrient cancer causing substances (e.g. fat) in the diet there are many non-nutrient and micronutrient putative carcinogens[3]. A particularly potent example is aflatoxin which is produced by molds which are quite common. They are known to contaminate

peanuts, corn, cotton seed and some tree nuts. Also nitrite and nitrates and nitrosamines (nitrosamines produced by some bacteria) may be found in some foods including beets, celery, lettuce and radishes. Mushrooms are delicious but may be potentially dangerous since they contain hydrazines which are carcinogenic and mutagenic. Plants synthesize a great variety of substances that have been called their "pesticides" to ward off bacteria, insects, etc. Bruce Ames has found that a great many of these compounds are carcinogenic and mutagenic[3]. We can ingest them directly from the plant or indirectly through the milk of animals that have eaten toxin-producing plants. Some of the most widespread of the known naturally occuring mutagens are the flavonoids. These are found in such good things to drink and eat as tea, coffee, cocoa, fruit jams, red wine, beer and vinegar. Other examples are: Black pepper (contains safrole, a known carcinogen), celery and parsley (contain furocoumarins). This list could go on for many pages, as Ames says "There is just an incredible variety of nature's pesticides, and they're present in very large amounts . . . and I got into this business because I was worried about man-made things."[3] Although much attention and concern has been paid to the presence of man-made pesticides in food little attention has been paid to these "natural pesticides" which Ames suspects may turn out to pose a greater risk than the synthetic pesticides. But before anything is done, much more research, particularly epidemiological studies and long term cancer studies in animals are needed in this area.

Although they will not be discussed, because of space limitation, other components of the diet may be associated with cancer. These include alcohol, food additives and environmental contaminants. Although there is some evidence linking these compounds to cancer it is generally concluded that they are not at all major determinants according to available evidence.

Assessing the Risk:

Although figuring the exact risk of various dietary components in the genesis of cancer is impossible, it may be useful to get a rough idea of the magnitude associated with diet. Even here the many factors to be taken into consideration make it a very "soft" scientific assessment. Nevertheless because of its importance a number of workers have computed the estimated risks and are in general agreement. Higginson and Muir[1] estimated that the proportion of cancer caused by "life style" (including diet) was 30% in men and 60% in women. Other studies have placed it higher at 40% of cancers in men and 60% of cancers in women in the United States as attributed to dietary factors alone[1]. More recently Doll and Peto have conducted an extensive review to estimate quantitatively the specific environmental determinants of cancer[1,4]. Although they stress the limitations of current knowledge they estimate that between 10% and 70% of cancers in the USA may be caused by components in the diet. They believe that dietary modifications might eventually result in a 35% reduction of deaths from cancer in the United States. If this estimate is correct diet would rank second after cigarette smoking as a determinant of cancer in North America.

Conclusion:

Much evidence from epidemiological studies and experiments in the laboratory suggest that various dietary factors have important causative and protective roles in carcinogensis. The goal of prevention of cancer through a chemical interference with the molecular chain reactions that lead to malignancy may be possible. This could be done directly by avoiding initiating and promoting substances or indirectly by taking chemicals that block these cellular processes rather than after-the-fact trying to undo the damage of cancer by other means[1,6].

Although some researchers do not believe that the information presently available is complete enough to make any strong dietary recommendations, others disagree. The National Research Council's Committee on Diet, Nutrition and Cancer has come out with a set of dietary guidelines that are both consistent with good nutrition and likely to reduce the risk of cancer. The committee is well aware that these guidelines are preliminary, and that they will need to be changed and focused as new research determines more precisely the dietary culprits that cause cancer.

Dietary Guidelines: (From the NRC guidelines[1] — slightly modified)

1. Reduce fat intake from 40% of total calories down to 30% (or less) of total calories. Red meats, dairy products and eggs are major sources of fat in the diet.
2. Eat more food with fiber. These include whole grains and fruits and vegetables.
3. Eat lots of food rich in beta-carotene: spinach, carrots, apricots and peaches. Eat cruciferous vegetables like broccoli, cabbage, brussels sprouts, etc.
4. Do not eat as much smoked, salted or nitrite preserved meat and fish. Also some forms of pickling produce high levels of N-nitroso compounds — avoid these foods when possible.
5. Consume alcohol in moderate amounts, if at all.
6. Although in the future it may be deemed useful to take supplements of some dietary compounds (e.g. Vitamin A and/or selenium) at the present time this is not recommended. This is not only because people seem to get enough in a well-balanced diet, but also because these substances are quite toxic in high doses.

Acknowledgements

I thank my dear wife Katherine (Yuen Kao) for help with this article.

References

1. National Research Council: *Diet, Nutrition and Cancer.* Washington: National Academy Press, 1982.
2. Creasey, W.A.: *Diet and Cancer.* Philadelphia: Lea & Febiger, 1985.
3. Ames, B.N.: *Dietary Carcinogens and Anticarcinogens.* Science *221* (1983), 1256-1263.
4. Willett, W.C., and MacMahon, B.: *Diet and Cancer: An Overview.* (Part one). New England Journal of Medicine, Vol. *310*, (No. 10) 633-639, March 8, 1984.
5. Willett, W.C., and MacMahon, B.: *Diet and Cancer: An Overview.* (Part two). New England Journal of Medicine, Vol. *310*, 697-703 (No. 11), March 15, 1984.
6. Blonston, G.: *Cancer: The New Synthesis-Prevention.* Science '84, September 1984. 36-39.
7. Roberts, L.: *Cancer Today: Origins, Prevention and Treatment.* Washington: National Academy Press, 1984.
8. Newell, G.R. (Editor): *Cancer Prevention in Clinical Medicine.* New York: Raven Press, 1983.
9. LeRiche, W.H.: *The Bottom Line: Ecology, Resources, Population, Nutrition and Medical Research.* February 1984. Paper was presented as part of seminar course in *Human Ecology* at the University of Toronto Medical School.

Percutaneous Transluminal Coronary Angioplasty as a Current Therapy in the Treatment of Coronary Artery Disease. – a review.

Jafna L. Cox, B.A. 8T8

Abstract

Percutaneous transluminal coronary angioplasty (PTCA) is a relatively new procedure, yet one which is being widely applied in the treatment of coronary heart disease (CHD). This review article discusses PTCA in terms of its method and application, indications and contraindications, mechanism and associated problems. PTCA and coronary artery bypass grafting (CABG) are compared, and the long-term prospects of PTCA in the treatment of CHD are considered.

Introduction

Unrecognized as a major health problem until the first decade of this century, atherosclerosis and its combined clinical sequelae have become the leading cause of death in industrialized countries. Since 1968, American mortality rates from coronary heart disease (CHD) have declined at an average rate of approximately 3% per year[1]. Despite this encouraging development, the disease remains of epidemic proportion. In the United States, where some 4.3 million people are thought to have a history of (CHD), it is responsible for over a million heart attacks and 640,000 deaths each year. With one in five males developing the disease before the age of 60, it is the primary cause of major disability in the prime of life. The economic cost has been close to $60 billion[2]. Canadian figures can be reasonably approximated as being a tenth as large.

Until an effective cure for atherosclerosis is developed, clinical management of patients continues to be aimed at maximizing cardiac function for as long as possible. In the decade which followed the description of coronary artery bypass grafting (CABG) by Favoloro[3], open heart surgery was the only alternative to medical therapy. This remains a useful palliative measure. Both the operative and the average annual mortality rate at five years are under 1.5%[2], long-term prognosis upwards of 10 years is favourable[4], and immediate symptomatic benefits are realized[2]. However, studies have failed to demonstrate that CABG offers any advantage over medical therapy in terms of prolonging life for patients with chronic stable angina of Canadian Cardiovascular Society Class I or II[2,5]. Moreover, some 15% of saphenous vein bypass grafts undergo severe occlusive changes within the first postoperative year[6]. Approximately 10% of patients with long-term follow-up have required reoperation[2,4]. Because repeat surgery is associated with a greater mortality and a higher frequency of complications than in the initial operation[7], any complementary interventions aimed at extending the period of palliation are of value.

One such measure is percutaneous transluminal coronary angioplasty (PTCA), a nonoperative procedure for enlarging the lumina of coronary arteries obstructed by atheromatous disease. The concept of medical dilatation is not new. The urethra was dilated by the Ancient Egyptians and Romans using reeds, while the first use of a ballon catheter was reported in the early 1800s for the same purpose[8]. However, it was the inadvertant transluminal recanalization of an occluded iliac artery during a routine abdominal aortogram that prompted Dotter and Judkins to describe, in 1964, the use of coaxial catheters to dilate atherosclerotic stenoses in peripheral vascular disease[9]. The development of a double-lumen catheter with a balloon at its tip ten years later by Grüntzig and Hopff foreshadowed the first application of PTCA in a human in 1977[10]. The purpose of this review is to discuss briefly the current status of this procedure.

Method

PTCA is a technologically sophisticated therapy whose basic requirements include the rapid visualization of the coronary circulation from several different projections, and high resolution monitoring of the course of the dilating catheter[11,12,13]. Briefly, arterial puncture is performed under local anesthetic. The insertion sheath is introduced, customarily into the femoral artery (Fig. 1). An appropriate guiding catheter is passed over a guide wire retrograde into the ascending aorta. A balloon catheter is advanced slowly within the guide catheter until the target vessel is reached and entered. After the stenosis is crossed, infusion of saline and contrast material into the balloon is begun for a number of seconds at a pump-controlled pressure. This usually results in enlargement of the arterial lumen. If the procedure is judged successful, the dilating catheter is removed and a repeat angiogram is obtained. After PTCA, the patient is monitored for signs or symptoms of myocardial ischemia. Telemetry is continued for a period of hours, while serial electrocardiograms and creatinine phosphokinase values are obtained.

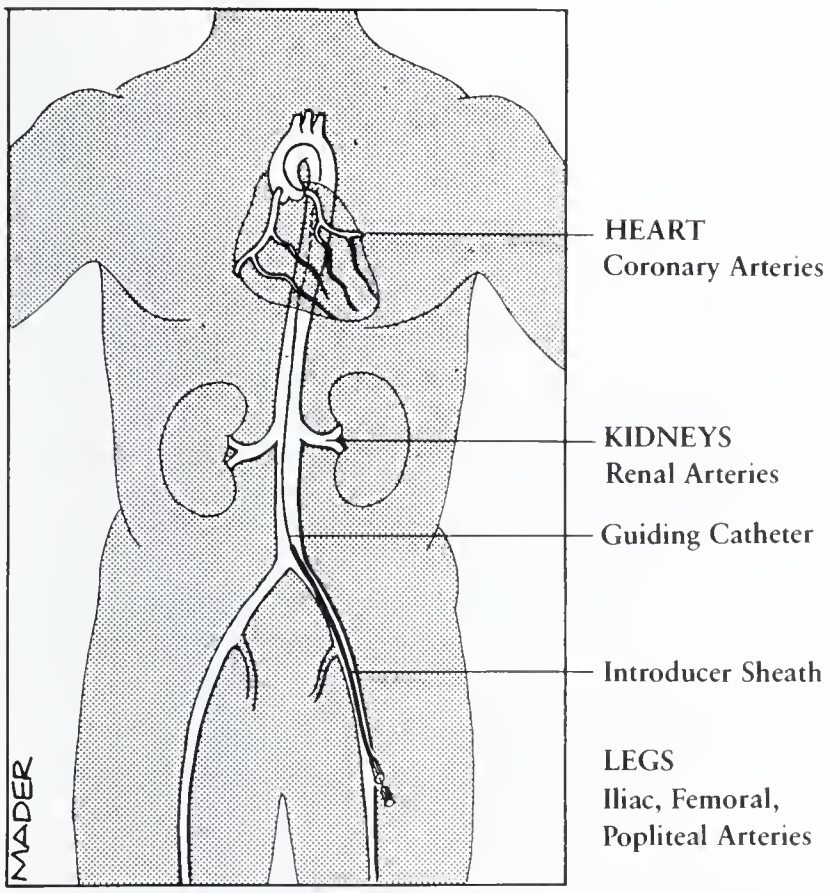


Figure 1. Arteries on which angioplasty can be routinely performed. Adapted from JN Purcell: *Angioplasty, a procedure in which a narrowed artery can be widened by inflation of a balloon-tipped catheter*, patient manual at Emory University Hospital, 1981.

Mechanism

Observations from numerous human and animal pathological specimens suggest that dilatation results primarily from plaque and arterial wall disruption[14,15]. Some 90% of the luminal area increase is due to disruption, less than 2% to compaction of plaque constituents, while the balance is the result of content extrusion[15].

Inflation of the dilating balloon within an atherosclerotic segment exerts a progressive expansile force which causes an initial extrusion of fluid from the atheroma. Continued expansion of the balloon brings mechanical stresses to a critical value. The essentially nondistensible plaque splits at its weakest point, with the tear extending to the intima and occasionally into the media[14-17] (Fig. 2). Tensile forces are directed along the circumference. This can cause commonly seen eccentric lesions to tear longitudinally at the junction of the plaque and arterial wall[15,17]. Endothelial desquamation, often observed in histological studies [16,18], results from the occurence of maximum stresses directly at the intimal surface. The elastic media and adventitia provide the only remaining resistance to the circumferential stretching of the vessel by the balloon once the splinting action of the nondistensible plaque has been removed. Prolonged inflations at pressures greater than 6 atmospheres can result in damage or necrosis of the medial muscle cells with permanent overstretching of the media[14,18]. Iatrogenic formation of an aneurysm is thus achieved. Excessive trauma to the arterial wall may predispose the vessel to spasm[19], intimal dissection[20], or rupture[21].

This "controlled injury" mechanism has important clinical implications. Because the atheroma continues to adhere to the vessel wall, fragmentation of the plaque is rare and embolization following coronary angioplasty is an infrequent event (<0.2%)[22]. Since longitudinal tears are colinear with blood flow, they are not subject to lifting forces as transverse tears would be. Therefore complications such as intimal flap formation and development of a dissecting aneurysm are uncommon. Disruption of the endothelial surface and exposure of the subendothelial connective tissue does predispose to rapid deposition of platelets and fibrin at the PTCA site[15,18]. The occurence of platelet thrombi can be minimized by use of intra-

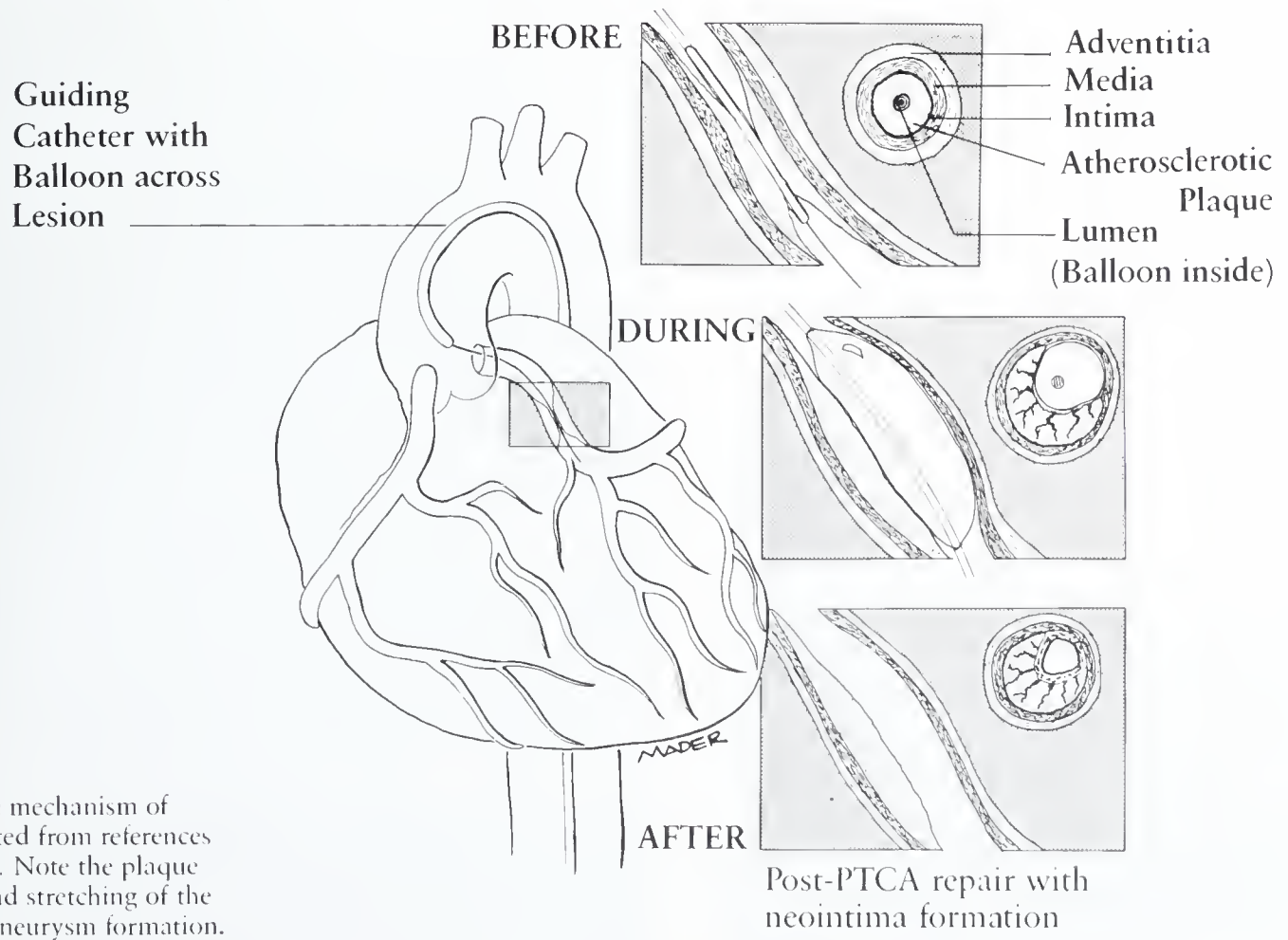


Figure 2. The mechanism of PTCA. Adapted from references (14) and (40). Note the plaque disruption and stretching of the media with aneurysm formation.

venous heparin during the procedure and long-term antiplatelet therapy following it. The contributions of other drugs given during the procedure remain speculative[2,3].

The healing process that occurs following PTCA is not yet understood. Studies in canine models suggest the formation of a neointima and the proliferation of collagen and monocytes into the media, a process similar to that observed following endarterectomy[14,18]. Essed et al. have postulated that intimal damage may initiate an excessive fibrocellular response and thereby accelerate atheromatous production[24]. This could account for the early recurrence of stenotic lesions in some patients within six months of a successful PTCA. However, a very normal appearance with a more smoothly lined vessel lumen may also be found on follow-up angiograms taken 6 months to 1 year later. A further increase in luminal size is often noted. It has been suggested that this may be the result of fibrous retraction[25], which is a part of the healing process, and/or progressive dilatation of the artery under the action of physiologic pressure[17].

Physiology

Atherosclerosis may deplete cardiac flow reserve capacity, severely compromising the ability of the system to respond appropriately to stress. Exertion can cause angina pectoris and an inadequate coronary blood flow response prompting a shift to anaerobic metabolism[26]. Successful PTCA results in a reduction of the flow-limiting stenosis and trans-stenotic pressure gradient. Myocardial perfusion is increased as assessed by thallium scintigraphy and exercise testing[26,27]. Left ventricular function is also improved, either by amelioration in the rate and extent of flow in early diastole, or by reduction or elimination of reversible myocardial ischemia[28]. Regional wall motion abnormalities after exercise are resolved in 90% of patients having such problems prior to the procedure[29]. Vascular reserve and alpha-adrenergic tone are reestablished, thereby restoring the ability of the coronary circulation to respond to stress[26,27,29].

Indications

Success in PTCA is defined as a 20% or greater gain in luminal diameter as assessed angiographically. It is a function of operator experience and patient selection, and can be enhanced by improvements in technique and equipment. A learning curve has been clearly demonstrated. Significant reduction in stenosis can now be expected in 70-90% of patients with a low complication rate (21% total, 9% serious) and 0.9% mortality (13,22).

The ideal candidate for PTCA, as initially proposed, has a single vessel, proximal, subtotal, concentric, noncalcified lesion (Table 1). He/she has normal left ventricular function and angina pectoris of recent onset, which is refractive to medical therapy, but is otherwise a candidate for CABG in the event that a complication occurs which requires surgical intervention[30]. Improvements in technology and technical expertise have considerably expanded these indications (Table 2). The advent of "steerable" guide wires, which can be manipulated to avoid side branches or to manoeuvre around sharp bends, has largely obviated problems posed by a circuitous coronary anatomy[31]. Balloon catheters with a variety of expanded diameters, lower deflated profiles, and the ability to withstand higher inflation pressures are available[32]. This has facilitated the dilatation of tighter, longer and more rigid stenoses. Lesions at bifurcations, or near large adjacent collaterals, used to pose a problem owing to the risk at angioplasty of occluding the neighbouring channel with redistributed vessel wall constituents. This can now be prevented by alternately inflating a balloon in each artery, thereby protecting the disease-free lumen against blockage[32,33]. Increased operator confidence has led to PTCA of tandem lesions as well as angioplasty of a number of diseased vessels during a single procedure[34]. Early results implied that this could be accomplished with rates of success and complication comparable to those experienced in treating single vessel disease[35]. Recently evaluated follow-up data suggest that such comparisons hold only when all significant proximal lesions are dilated[36,37]. Clearly, patients with multiple vessel disease treated by PTCA and incompletely revascularized are prone to a higher incidence of recurrent angina, due largely to the vessels which remain compromised.

During its nine years of clinical use, coronary angioplasty has proved to be an appropriate and effective treatment for stable and unstable angina[38,39]. Patients with unstable angina form the largest group undergoing PTCA[38]. Immediate cardiac catheterization and PTCA may be safer and more cost-effective than medical therapy and hospitalization aimed at "stabilizing" the patient's condition[40]. Although technically feasible[41], PTCA is not

Table 1. The Ideal Candidate For PTCA.

— Single vessel disease
— Proximal, subtotal, concentric stenosis
— Noncalcified lesion
— Normal left ventricular function
— Angina pectoris of recent onset
— Refractive to medical therapy
— Surgical candidate

Table 2. Expanded Indications For PTCA.

— Multivessel disease
— Distal, eccentric or calcified lesions
— Lesions at vessel bifurcations
— Unstable angina
— Acute MI
— Stenosed bypass grafts

recommended in the treatment of variant angina because symptoms due to coronary spasm usually persist or recur, often with restenosis[42].

The effectiveness of intracoronary streptokinase in restoring coronary flow in patients with acute myocardial infarction (MI) is currently being assessed. Subsequent hemostatic problems are inherent to this therapy[43]. Moreover, severe residual stenosis may jeopardize any expected wall motion improvement[44]. PTCA has therefore been used in conjunction with coronary thrombolysis to dilate severe residual stenoses. This therapeutic strategy aims to enhance wall motion recovery and lessen the risks of reocclusion[44,45,46]. More recently, PTCA without prior thrombolytic therapy has been advocated as a "definitive" treatment for acute MI[46,47]. One advantage of this technique is that emergency CABG could be performed without concern for a treatment-induced bleeding diathesis.

When CABG is indicated, its applicability may be limited by distal coronary artery disease. This can be addressed with angioplasty, which is developing into a valuable adjunct without significant added surgical risk[48]. More useful is the application of PTCA to recanalize stenosed bypass grafts[49]. There is probably a higher rate of restenosis following successful angioplasty of a bypass graft[13,49,50]. There is also an increased mortality in patients with a previous CABG who are treated with PTCA[13,35]. However, the risks involved in a reoperation are far greater, with mortality increased as much as four-fold over that of the initial surgery[7]. Angioplasty is safe by comparison, and is more easily performed. It also allows patients to defer a second operation. While experience of PTCA on stenosed grafts remains limited, the reported success rate varies widely between 75% and greater than 90%[51].

Contraindications

Although recent advances have permitted an expansion of the admission criteria, PTCA is far from universally applicable (Table 3). Total occlusion of a coronary artery, while treatable with angioplasty[52], probably carries a higher risk of vessel perforation or of thrombus formation[35]. Other relative contraindications are left main coronary artery stenosis in which a patient's myocardium may be maximally compromised should a complication occur, or poor left ventricular function which may reduce survivability if emergency surgery is required[25]. Coronary artery spasm without underlying stenosis remains a general contraindication. Dilatation of vessel segments prone to spasm is investigational, and treatment with nitrates or calcium antagonists where possible is recommended instead[23,25,35]. PTCA is also not recommended in the treatment of mild stenosis. Patients with vessels obstructed by less than 60% who undergo coronary angioplasty appear to be at a heightened risk for MI and emergency surgery. The disease process may even be accelerated[53].

Data from the National Heart, Lung, and Blood Institute's PTCA registry in the United States have identified a number of groups with low success rates at PTCA (Table 4). These include patients over 60 years of age, those with previous CABG, those with left main disease, those who required PTCA for a bypass graft, patients with angina for longer than 6 months, and women[22,35,54]. Not only is the PTCA success rate 5% lower in women than in men, but they are more than twice as likely to require emergency surgery (14.6% vs. 6.6%). Indeed, female gender is the only identified risk factor for PTCA-related deaths, with women over two-and-a-half times as likely to die during the procedure as men (1.8% vs. 0.7%)[54]. These findings may be due to the greater age and more severe symptomatic status in women referred for coronary angioplasty.

Table 3. Absolute Contraindications To PTCA.

— Left mainstem coronary artery stenosis
— Poor left ventricular function
— Coronary artery spasm without underlying stenosis

Relative Contraindications To PTCA

— Mild (<60%) stenosis
— Total vessel occlusion
— Variant angina

Table 4. Groups With Low Success Rates At PTCA.

— Patients over 60 years of age
— Patients with previous CABG
— Patients with left mainstem disease
— Patients who require PTCA for bypass graft(s)
— Patients with angina longer than 6 months
— Women

Complications

As with any invasive procedure, complications persist. These arise as a result of coronary vascular events – dissection, occlusion, spasm, coronary embolism, perforation, rupture, MI or prolonged angina – in under 14% of patients[22] (Table 5). The most frequent complaint is angina during or immediately following the procedure (6.8%). The clinical course is usually benign[55], although 7% of patients experience prolonged angina with some 25% of these subsequently evolving a myocardial infarction[22]. Emergency myocardial revascularization therefore remains the accepted therapy for immediate or delayed myocardial ischemia[55,56].

Such emergency surgery is ultimately required in 5-6% of patients undergoing PTCA. The two major precipitating factors are acute occlusion and coronary artery dissection which each occur in approximately 5% of patients[22]. Myocardial infarction may be secondary to

Table 5. Major Complications At PTCA (22).
From data collected by 105 contributing centers on 3,079 patients enrolled in the NHLBI PTCA Registry between September 1977 and September 1982.

Event	Number of Patients	%
Total complications	652	21
Coronary vascular* or ischemic** events	418	13.6
Major complications +	280	9.1
Prolonged angina	211	6.8
Myocardial infarction	170	5.5
Coronary occlusion	151	4.9
Coronary dissection	135	4.3
Coronary spasm	130	4.2
CABG (without death/MI)	106	3.4
Death	29	.9
Coronary embolism	5	>.2
Coronary perforation	2	>.2
Coronary rupture	1	>.2

* i.e. Dissection, occlusion, spasm, embolism, perforation and rupture.
** i.e. MI or prolonged angina. + i.e. MI, emergency surgery or death.

Acute coronary vascular or ischemic events were sustained by 418 patients. Major complications occurred in 197 of the 323 individuals (62%) who had acute coronary vascular events, representing 68% of all major complications.

either of these. When arterial occlusion occurs in angioplasty patients, it is often as a result of intracoronary thrombus formation, coronary artery spasm, or intimal flap formation[57,58]. In many cases the vessel can be reopened with nitrates, calcium antagonists, thrombolytic therapy, or repeat PTCA[58]. Coronary artery dissection may be a reflection of the mechanism of successful PTCA. However, it can also lead to compromised blood flow. The only effective treatment is intra-aortic balloon pump counterpulsation to stabilize the patient hemodynamically, followed by emergency surgery[56]. Clinical profiles do not predict an increased likelihood of surgical intervention, although a complicated angiographic morphology of the coronary lesion may predispose to dissection or occlusion[58]. Other complications, including hypotension, arrhythmias, and local femoral hematoma formation appear with equal frequency as with routine cardiac catheterization and coronary angiography[13,25]. Distal coronary embolization after PTCA is rare, clinically and experimentally[59]. While slight elevation of CPK without ECG changes is occasionally observed after PTCA[60], this is more likely the result of small areas of infarction caused by platelet microemboli rather than fragmented plaque constituents. Whatever its etiology, this occurence does not seem to be important in terms of cardiac function[60].

PTCA carries a smaller than 1% risk of mortality which appears to be related to the extent of the disease and to the speed with which patients can be operated on when problems develop. Therefore, it is imperative that an operating room and surgical team be available when coronary angioplasty takes place[13,56]. Patients in whom coronary angioplasty has failed and who go on to CABG are at a higher risk of mortality and intraoperative complications; perhaps 3-4 times that associated with elective surgery[23,61,62]. This is owing in part to the emergency circumstances of the operation and the increased likelihood of MI. However, the functional outcome is not compromised[63].

Restenosis

Because of the high success rate and low complication rate of PTCA, restenosis after a successful procedure is the most persistent major concern. Reported rates of recurrence vary from 15-43%[11,25,35,50]. The most commonly used angiographic definition of restenosis is loss of 50% of the previous gain in luminal diameter[50]. The incidence is highest within the first 5 months after angioplasty with most patients manifesting symptoms of recurrent myocardial ischemia by the third month[50,64]. Asymptomatic restenosis, although uncommon, can be devastating when it occurs owing to the potential for late death[64]. Rosing et al., reporting on a small clinical series, found that 95% of individuals with a patent PTCA site 6 months after PTCA remained free of clinically significant obstruction after 3 years[65]. Further improvement in the angiographic appearance of the lesion was also observed in seven of fourteen patients investigated.

Factors affecting restenosis have not yet been definitely identified, however a number of etiologies may be proposed[66,67]. Studies suggest that the use of higher balloon dilatation pressure results in an improved hemodynamic result[68] and lower restenosis rates[64]. Excessive pressure may also traumatize the vessel wall and predispose the coronary artery to spasm[19]. A number of predictors of restenosis have been suggested, including the severity of the initial lesion[68], severity of angina, male sex, no history of prior MI, angioplasty of bypass graft stenosis[50], old age, lesions involving branches, and lesions requiring more than 9 dilatations per segment[69]. No definitive cause and effect relationship has as yet been established between any of these variables and restenosis.

In order to guard against the possibility of recurrent disease, all PTCA patients should have objective measurements of coronary insufficiency performed, such as a stress test with thallium scintigraphy and/or an exercise ECG, prior to PTCA. This allows comparison with follow-up angiography and noninvasive testing to assess improvement or recurrence[25]. Should a vessel restenose, a

Left anterior oblique view of the right coronary artery with a subtotal occlusion in the proximal-third.

Before PTCA.

After successful PTCA.

At two-months restudy, showing severe restenosis.

second PTCA can be performed with a higher success rate and lower risk than the initial procedure[70]. Patients are usually referred for CABG if the stenosis reappears for a third time[11]. Experience has shown that any stenosis occuring within 3 months of a successful PTCA is best treated surgically[2,3].

PTCA vs. CABG

It is unlikely that PTCA will ever succeed in replacing bypass surgery. Patients with totally occluded vessels, diffuse disease, or left main coronary artery stenosis will remain primarily candidates for CABG[40]. PTCA patients tend to have a shorter history of angina, fewer prior MIs, and better LV function than those scheduled for surgery[61]. Most centers report that only 15-20% of their bypass patients are suitable for angioplasty[11,71]. Nevertheless, because this still represents a large number of individudals, the impact of PTCA is significant – it is estimated that some 85,000 procedures were performed in the United States in 1984[71]. Although the functional outcomes of PTCA and CABG are comparable[72], angioplasty involves less pain and suffering. Even when primary failure and late restenosis rates are taken into account, PTCA can be 43% less expensive in the treatment of single vessel disease[73,74,75].

Since treatment of restenosis is the major factor increasing PTCA costs, further reduction in expense may be expected if restenosis rates are improved[75]. In the United States, application of PTCA may result in savings in excess of $170,000,000 annually[73]. More critical observers have disputed such estimates although even they concede a 15% cost difference[76]. Studies of long follow-up intervals are needed to assess the durability of PTCA and thus its cost-effectiveness. Certainly PTCA patients have a shorter hospital stay (4 +/− 2 vs. 12 +/− 5 days), show a higher employment rate (79% vs. 69%), and return to work on average seven weeks earlier than CABG patients[73]. They also show a higher productivity[77].

This is not to suggest that coronary angioplasty and bypass surgery should be considered competitive procedures. Both are temporizing and can therefore be employed in tandem over the total course of a patient's treatment period. PTCA may be a useful adjunct at the time of operation, or later in treating disease progression. Patients considered unsuitable for surgery because of unfavourable disease distribution or high operative risk may, in some circumstances, be offered PTCA. Repeat angioplasty can be performed if restenosis recurs. Dilatation may delay an operation, but it is unlikely to preclude one in the event of failure. Younger, more active patients will less likely be satisfied with medical therapy. Yet they will probably outlive the effectiveness of bypass surgery, with the prospect of reoperation in 5-10 years because of graft closure or progression of disease. PTCA can be used to delay CABG so that only one operation may be necessary[40]. Elderly patients, over 70 years of age, appear to be less symptomatic following CABG than PTCA[78]. However, they run an increased surgical risk of stroke and operative mortality. Their postoperative convalescence is slower, and the incidence of illness in other organ systems is higher. They are also less likely to be able to shoulder the financial burden of CABG, at least outside Canada. For all these reasons, PTCA is especially advantageous in older age groups[79].

Future Prospects

There seems little doubt that percutaneous transluminal coronary angioplasty, now approaching its tenth year of clinical use, is an established and increasingly accepted therapy for the treatment of coronary artery disease. Although still under evaluation, and with its long-term impact as yet unknown, the procedure nevertheless appears to promise a sustained result. The most important task for the present is to reduce the high restenosis rate associated with roughly a third of all coronary angioplasties performed. Indeed, unless this is

achieved to a significant degree, the cost-benefit of PTCA as compared to CABG may increasingly be questioned. A better understanding of how the vessel wall responds to balloon-induced trauma may allow for the development of technical or pharmacologic strategies with which to address this concern. Equally important is the need to assess more stringently the effectiveness of PTCA. Long-term follow-up data are now being analysed at centres across North America. Mock et al.[80] have recently proposed patient subgroups suitable for randomization; there seems to be a need to compare PTCA with CABG and medical therapy in prospective, randomized trials, so as to define better their respective roles in the treatment of coronary heart disease.

References

1. Stamler J: The marked decline in coronary heart disease mortality rates in the United States, 1968-1981; summary of findings and possible explanations, *Cardiology* 72: 11-22, 1985.
2. CASS Principal Investigators and their Associates: Coronary artery surgery study (CASS): A randomized trial of coronary artery bypass surgery. Survival data, *Circulation* 68: 939-50, 1983.
3. Favaloro RG: Saphenous vein autograft replacement of severe segmental coronary artery occlusion: Operative technique, *Ann Thorac Surg* 5: 334-9, 1968.
4. Laird-Meeter K, Penn OCKM, Haalebos MMP, et al.: Survival in 1041 patients with consecutive aorto-coronary bypass operations, *Eur Heart J* 5: 35-42, 1984.
5. CASS Principal Investigators and their Associates: Coronary Artery Surgery Study (CASS): A randomized trial of coronary artery bypass surgery. Quality of life in patients randomly assigned to treatment groups, *Circulation* 68: 951-60, 1983.
6. Bourassa MG, Enjalbert M, Campeau L, et. al.: Progression of atherosclerosis in coronary arteries and bypass grafts: Ten years later, *Am J Cardiol* 53: 102c-107c, 1984.
7. Gonzales-Santos JM, Ennabli K, Grondin C: Repeated coronary artery bypass grafting in patients with patent atherosclerotic grafts: A special challenge, *Thorac Cardiovasc Surg* 32: 346-49, 1984.
8. Abele JE: Balloon catheters and transluminal dilatation: Technical considerations, *AJR* 135: 901-6, 1980.
9. Dotter CT, Judkins MP: Transluminal treatments of arteriosclerotic obstruction: Description of a new technic and a preliminary report of its application, *Circulation* 30: 654-70, 1964.
10. Grüntzig AR, Senning A, Siegenthaler WE: Nonoperative dilatation of coronary artery stenosis: Percutaneous transluminal coronary angioplasty, *N Engl J Med* 301: 61-8, 1979.
11. Hall D, Gruentzig A: Percutaneous transluminal coronary angioplasty: Current procedure and future direction, *AJR* 142: 13-16, 1984.
12. Libow M, Gruentzig AR, Greene L: Percutaneous transluminal coronary angioplasty, *Curr Probl Cardiol* 10: 1-55, 1985.
13. William VL: Percutaneous transluminal coronary angioplasty, a 1985 perspective, *Circulation* 71: 189-92, 1985.
14. Castenada-Zuniga WR, Formanek A, Tadavarthy M, et. al.: The mechanism of balloon angioplasty, *Radiology* 135: 565-71, 1980.
15. Kinney TB, Chin AK, Rurik GW, et. al.: Transluminal angioplasty: A mechanical-pathophysiological correlation of its physical mechanisms, *Radiology* 153: 85-9, 1984.
16. Pasternak RC, Baughman KL, Fallon JT, et. al.: Scanning electron microscopy after coronary transluminal angioplasty of normal canine coronary arteries, *Am J Cardiol* 45: 591-98, 1980.
17. Mizuno K, Kurita A, Imazeki N: Pathological findings after percutaneous transluminal coronary angioplasty, *Br Heart J* 52: 588-90, 1984.
18. Zollikofer CL, Solomonowitz E, Sibley R, et. al.: Transluminal angioplasty evaluated by electron microscopy, *Radiology* 153: 369-74, 1984.
19. Walton J, Colfer HJ, Kirsh M, et. al.: Coronary artery spasm – A complication of percutaneous transluminal angiopasty (abstr.), *J Am Coll Cardiol* 1: 643, 1983.
20. Waller BF, Dillon JC, Crowley MJ: Plaque hematoma and coronary dissection with percutaneous transluminal angioplasty (PTCA) of severely stenotic lesions: Morphologic coronary observations in 5 men within 30 days of PTCA (abstr.), *Circulation* 68: III-144, 1983.
21. Meier B: Benign coronary perforation during percutaneous transluminal coronary angioplasty, *Br Heart J* 54: 33-5, 1985.
22. Cowley MJ, Dorros G, Kelsey SF, et. al.: Acute coronary events associated with percutaneous transluminal coronary angioplasty, *Am J Cardiol* 53: 12c-16c, 1984.
23. Council on Scientific Affairs: Percutaneous transluminal coronary angioplasty, *JAMA* 251: 764-68, 1984.
24. Essed CE, Brand Mvd, Becker AE: Transluminal coronary angioplasty and early restenosis: Fibrocellular occlusion after wall laceration, *Br Heart J* 49: 393-96, 1983.
25. Block PC: Percutaneous transluminal coronary angioplasty, in Connor WE, Bristow JD (eds.), *Coronary Heart Disease: Prevention, Complications and Treatment*, Philadelphia, J.B. Lippincott, 1985, 405-18.
26. Rentrop PK, Cohen M, Blamke H, et. al.: Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects, *J Am Coll Cardiol* 5: 587-92, 1985.
27. Okada RD, Lim YL, Boucher CA, et. al.: Clinical, angiographic, hemodynamic, perfusional and functional changes after one-vessel left anterior descending coronary angioplasty, *Am J Cardiol* 55: 347-56, 1985.
28. Weiss AT, Gotsman MS, Shefer A, et. al.: Improvement in regional ventricular function after percutaneous transluminal coronary angioplasty, *Int J Cardiol* 5: 299-311, 1984.
29. Kent KM, Bonow RO, Rosing DR, et. al.: Improved myocardial function during exercise after successful percutaneous transluminal coronary angioplasty, *N Engl J Med* 306: 441-46, 1982.
30. Weaver WF, Myler RK, Sheldon WC, et. al.: Guidelines for physician performance of percutaneous transluminal coronary angioplasty, *Cathet Cardiovasc Diagn* 11: 109-12, 1985.
31. Gruentzig AR, Meier B: Current status of dilatation catheters and guiding systems, *Am J Cardiol* 53: 92c-93c, 1984.
32. Meier B: Kissing balloon coronary angioplasty, *Am J Cardiol* 54: 918-20, 1984.
33. Pinkerton CA, Slack JD, Tassel JWv, et. al.: Angioplasty for dilatation of complex coronary artery bifurcation stenoses, *Am J Cardiol* 55 (Part 1 of 2): 1626-28, 1985.
34. Dorros G, Stertzer SH, Cowley MJ, et. al.: Complex coronary angioplasty: Multiple coronary dilatations, *Am J Cardiol* 53: 126c-30c, 1984.
35. Kent KM, Bentivoglio LF, Block PC, et. al.: Longterm efficacy of percutaneous transluminal coronary angioplasty (PTCA): Report from the National Heart, Lung, and Blood Institute PTCA registry, *Am J Cardiol* 53: 27c-31c, 1984.
36. Mabin TA, Holmes DR, Smith HC, et. al.: Follow-up clinical results in patients undergoing percutaneous transluminal coronary angioplasty, *Circulation* 71: 754-60, 1985.
37. Cowley MJ, Vetrovec GW, DiSciascio G, et. al.: Coronary angioplasty of multiple vessels: short-term outcome and long-term results, *Circulation* 72: 1314-1320, 1985.
38. Feyter PJ, Serruys PW, Brand Mvd, et. al.: Emergency coronary angioplasty in refractory unstable angina, *N Engl J Med* 313: 342-46, 1985.
39. Meyer J, Schmitz H-J, Kiesslich T, et. al.: Percutaneous transluminal coronary angioplasty in patients with stable and unstable angina pectoris: Analysis of early and late results, *Am Heart J* 106: 973-80, 1983.
40. Hollman J: Coronary angioplasty. A procedure that has 'come of age', *J Postgrad Med* 75: 137-51, 1984.
41. Corcos T, David PR, Bourassa MG, et. al.: Percutaneous transluminal coronary angioplasty for the treatment of variant angina, *J Am Coll Cardiol* 5: 1046-54, 1985.
42. Leisch F, Herbinger W, Brucke P: Role of percutaneous transluminal coronary angioplasty in patients with variant angina and coexistant coronary stenosis refractory to maximal medical therapy, *Clin Cardiol* 7: 654-59, 1984.
43. Rentrop PK: Thrombolytic therapy in patients with acute myocardial infarction, *Circulation* 71: 627-31, 1985.
44. Sheehan FH, Brown BG, Mathey DG, et. al.: Effect of severe residual stenosis on recovery of function after streptokinase (abstr.), *J Am Coll Cardiol* 3: 526, 1984.
45. Serruys PW, Wijns W, Brand Mvd, et. al.: Is transluminal coronary angioplasty mandatory after successful thrombolysis? Quantitative coronary angiographic study, *Br Heart J* 50: 257-65, 1983.
46. Holmes DR Jr, Smith HC, Vliestra RE, et. al.: Percutaneous transluminal coronary angioplasty, alone or in combination with streptokinase therapy, during acute myocardial infarction, *Mayo Clin Proc* 60: 449-56, 1985.
47. Sriram R, Mullen GM, Foschi A, et. al.: Percutaneous transluminal coronary angioplasty in acute myocardial infarction without prior thrombolytic therapy, *Am J Cardiol* 55: 842-43, 1985.
48. Roberts AJ, Faro RS, Feldman RL, et. al.: Preliminary experience with intraoperative transluminal balloon-catheter dilation and coronary artery bypass grafting for the treatment of symptomatic diffuse coronary artery disease, *J Thorac Cardiovasc Surg* 86: 435-40, 1983.
49. Douglas JS Jr, Gruentzig AR, King SB III, et. al.: Percutaneous transluminal coronary angioplasty in patients with prior coronary bypass surgery, *J Am Coll Cardiol* 2: 745-54, 1983.
50. Holmes DR, Vliestra DE, Smith HC, et. al.: Restenosis after percutaneous transluminal coronary angioplasty (PTCA): A report from the PTCA registry of the National Heart, Lung, and Blood Institute, *Am J Cardiol* 53: 77c-81c, 1984.
51. Gamal ME, Bonnier H, Michels R, et. al.: Percutaneous transluminal angioplasty of stenosed aortocoronary bypass grafts, *Br Heart J* 52: 617-20, 1984.
52. Serruys PW, Heyndrickx GR, Feyter PJd, et. al.: Elective PTCA of totally occluded coronary arteries not associated with acute MI (abstr.), *Eur Heart J* 5: 57, 1984.

53. Ischinger T, Gruentzig AR, Hollman J, et. al.: Should coronary arteries with less than 60% diameter stenosis be treated by angioplasty?, *Circulation* 68: 148-54, 1983.
54. Cowley MJ, Mullin SM, Kelsey SF, et. al.: Sex differences in early and long-term results of coronary angioplasty in the NHLBI PTCA registry, *Circulation* 71: 90-7, 1985.
55. Danchin N, Cuilliere M, Cherrier F: Transient acute ischemic episodes during or immediately after percutaneous transluminal coronary angioplasty, *Eur Heart J* 5: 362-5, 1984.
56. Murphy DA, Craver JM, Jones EL, et. al.: Surgical management of acute myocardial ischemia following percutaneous transluminal coronary angioplasty. Role of the intra-aortic balloon pump, *J Thorac Cardiovasc Surg* 87: 332-39, 1984.
57. Ischinger T, Zack P, Aker U: Acute coronary occlusion during balloon angioplasty due to intracoronary thrombus and coronary spasm: A reversible complication, *Am Heart J* 107: 1271-75, 1984.
58. Mabin TA, Holmes DR, Smith HC, et. al.: Intracoronary thrombus: Role in coronary occlusion complicating percutaneous transluminal coronary angioplasty, *J Am Coll Cardiol* 5: 198-202, 1985.
59. Sanborn TA, Faxon DP, Waugh D, et. al.: Transluminal angioplasty in experimental atherosclerosis. Analysis for embolization using an in vivo perfusion system, *Circulation* 66: 917-22, 1982.
60. Jae KO, Shub C, Ilstrup DM, et. al.: Creatine kinase release after successful percutaneous transluminal coronary angioplasty, *Am Heart J* 109: 1225-31, 1985.
61. Cowley MJ, Dorros G, Kelsey SF, et. al.: Emergency coronary bypass surgery after coronary angioplasty: The National Heart, Lung, and Blood Institute's percutaneous transluminal coronary angioplasty registry experience, *Am J Cardiol* 53: 22c-26c, 1984.
62. Jones EL, Murphy DL, Craver JM: Comparison of coronary artery bypass surgery and percutaneous transluminal coronary angioplasty including surgery for failed angioplasty, *Am Heart J* 107: 830-5, 1984.
63. Meier B, Gruentzig AR, Siegenthaler WE, et. al.: Long-term exercise performance after percutaneous transluminal coronary angioplasty and coronary artery bypass grafting, *Circulation* 68: 796-802, 1983.
64. Levine S, Ewels CJ, Rosing DR, et. al.: Coronary angioplasty: Clinical and angiographic follow-up, *Am J Cardiol* 55: 673-76, 1985.
65. Rosing DR, Kent KM, Bonow RO, et. al.: Three-years anatomic and functional follow-up after successful percutaneous transluminal coronary angioplasty (abstr.), *J Am Coll Cardiol* 3: 470, 1984.
66. Cox JL, Gotlieb AI: Restenosis following percutaneous transluminal angioplasty: clinical, physiologic and pathological features, *CMAJ* 134: 1129-1132, 1986.
67. Moore S: Restenosis following percutaneous transluminal angioplasty (letter), *CMAJ* 135: 101, 1986.
68. Meier B, Gruentzig AR, King SB, et. al.: Higher balloon dilatation pressure in coronary angioplasty, *Am Heart J* 107: 619-27, 1984.
69. Scholl JM, David PR, Chaitman BR, et. al.: Recurrence of stenosis following percutaneous transluminal coronary angioplasty (abstr.), *Circulation* 64: IV-193, 1981.
70. Williams DO, Gruentzig AR, Kent KM, et. al.: Efficacy of repeat transluminal coronary angioplasty for coronary restenosis, *Am J Cardiol* 53: 32c-35c, 1984.
71. Block PC: Emergency surgery after percutaneous transluminal coronary angioplasty: he who calls the tune may have to pay the piper, *Ann Thorac Surg* 40: 1, 1985.
72. Acinapura AJ, Cunningham JN, Jacobowitz IJ, et. al.: Efficacy of percutaneous transluminal coronary angioplasty compared with single-vessel bypass, *J Thorac Cardiovasc Surg* 89: 35-41, 1985.
73. Jang GC, Block PC, Cowley MJ, et. al.: Relative cost of coronary angioplasty and bypass surgery in a one-vessel disease model, *Am J Cardiol* 53: 52c-55c, 1984.
74. Kelly ME, Taylor GJ, Moses HW, et. al.: Comparative cost of myocardial revascularization: Percutaneous transluminal angioplasty and coronary artery bypass surgery, *J Am Coll Cardiol* 5: 16-20, 1985.
75. Reeder GS, Krishan I, Nobrega FT, et. al.: Is percutaneous coronary angioplasty less expensive than bypass surgery?, *N Engl J Med* 311: 1157-62, 1984.
76. Kouchoukos NT: Percutaneous transluminal coronary angioplasty: a surgeon's view, *Circulation* 72: 1144-1147, 1985.
77. Holmes DR, Raden MJv, Reeder GS, et. al.: Return to work after coronary angioplasty: A report from the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry, *Am J Cardiol* 53: 48c-51c, 1984.
78. McCallister BD, Hartzler GO, Reed WA, et. al.: Percutaneous transluminal coronary angioplasty in elderly patients: A comparison with coronary artery bypass surgery (abstr.), *J Am Coll Cardiol* 1: 656, 1983.
79. Zaidi AR, Hollman J, Franco I, et. al.: Coronary angioplasty: Can you refer older patients? *Geriatrics* 40: 38-44, 1985.
80. Mock MB, Reeder GS, Schaff HV, et. al.: Percutaneous transluminal coronary angioplasty versus coronary artery bypass: isn't it time for a randomized trial?, *N Engl J Med* 312: 916-19, 1985.

THE UNIVERSITY OF TORONTO

MEDICAL BOOKSTORE

Textbooks for all subjects

Comprehensive reference books
and general interest titles.

Complete review manuals in Medicine and Nursing

- Ask for our free catalogue
- free special order service

OPEN: MONDAY — FRIDAY 8.45 am — 6.00 pm
SATURDAY 11.00 am — 5.00 pm

LOCATION: 214 COLLEGE STREET
(COLLEGE & ST. GEORGE)

TEL: 586-7913

Poorly Resolving Pneumonia with Cavitation

Charles K. Chan, M.D., F.R.C.P.(C) *
Robert H. Hyland, M.D., F.R.C.P.(C) *
Donald P. Jones, M.D. F.R.C.S.(C) *
Robin R. Gray, M.D., F.R.C.P.(C) *

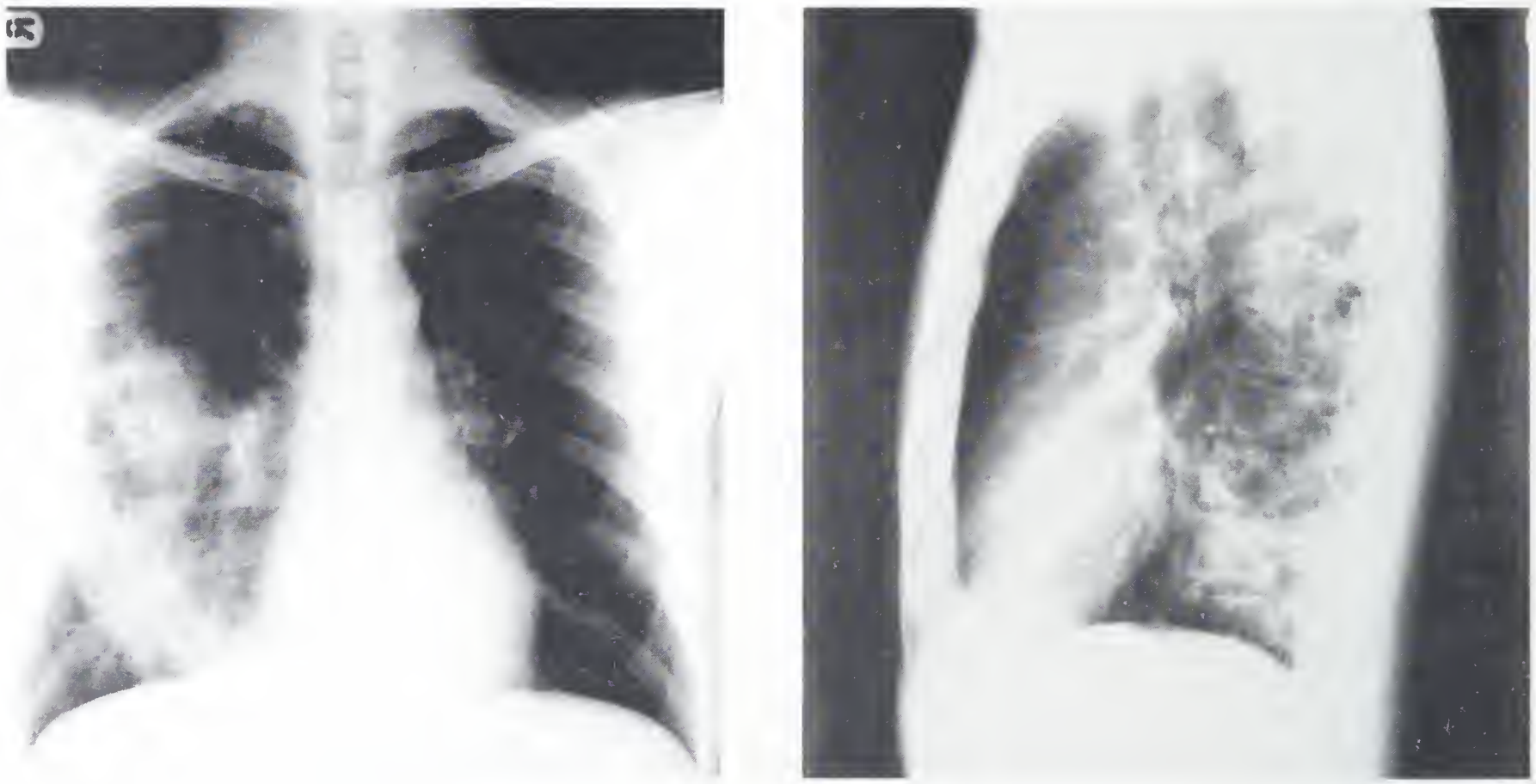


Figure (1a & b)
PA and lateral chest films show extensive consolidation in the right lower lung zone. Several lucencies suggesting cavities are seen on the lateral view overlying the spine.

Case

A 30 year old Chinese man presented to his family physician in January 1984 because of a 1 week history of fever, chills and nonproductive cough. Past history included tuberculosis exposure in 1981 and his tuberculin skin test was positive at that time. A chest roentgenogram (CXR) apparently showed a "scar" in his right lung in 1981 but he never received Isoniazid prophylaxis. Physical examination was unremarkable, specifically there were no crackles, wheeze or signs of consolidation, however, his CXR on this occasion

**Departments of Medicine, Surgery and Radiology, The Wellesley Hospital, Toronto, Canada.*

showed a right lower lung infiltrate consistent with lobar pneumonia.

He was given a 10-day course of Ampicillin with some improvement in his pulmonary symptoms. However, he relapsed 1 week later with cough, haemoptysis, night sweats and dyspnea on exertion. A CXR at this time showed extension of the right lung infiltrate (Fig. 1a & b). He was admitted to hospital for further investigation and treatment. Numerous samples of sputum revealed no specific microbiological pathogen. Because of persistent haemoptysis, a bronchoscopic examination was performed. The only abnormal finding was inflammation and blood at the orifice of the superior segment of the right lower lobe. Bronchial washings and brushings were negative for microbiology and cytology. A chest CT scan showed multiple cystic cavities in the right lower lobe region. A percutaneous transthoracic needle aspiration was also negative for microbiology and cytology. The Infectious Disease Service interpreted the clinical presentation as highly probable for pulmonary tuberculosis and recommended initiation of triple therapy (Isoniazid, Rifampin and Ethambutol). The cough and haemoptysis gradually resolved during the first week of triple therapy. A CXR taken 7 days after starting anti-tuberculous therapy, showed complete resolution of his pulmonary infiltrate.

Two months later, all T.B. and fungal cultures had been reported as negative except for a few colonies of an atypical mycobacterium. In order to clarify the pulmonary abnormality in the right lower lung region, a right sided brochogram was done. The bronchogram showed anterior displacement of the right lower lob bronchial tree and there was no bronchial communication between the posterior inferior area of the right hemithorax (where the cavities were located) and the remainder of the right lung. (Fig. 2a & b)

What is your diagnosis?

MEDICAL MART
SUPPLIES LIMITED

1224 DUNDAS STREET E., UNIT 28
MISSISSAUGA, ONTARIO, CANADA
L4Y 4A2 PH. (416) 276-4800
MEDIWATTS 1-800-268-2848 (ONT. ONLY),
TELEX 06-960218

PHYSICIAN STUDENTS SUPPLIES
A ONE STOP SUPERMARKET
FOR ALL YOUR OFFICE NEEDS

- Welch Allyn Diagnostic
- Treatment Cabinets
- Taylor & Brum B P Units
- Littmann Stethoscope
- B-D Syringes & Needles
- Step Stools
- Surgeon's Stools
- Exam Tables
- Scales
- Dressings

Let our experienced trade professional assist in your requirements

VISIT OUR LARGE MODERN SHOWROOM

HOURS: 9:00 - 5:00 Mon., Tues., Wed.
9:00 - 7:00 Thurs. 9:00 - 6:00 Fri.

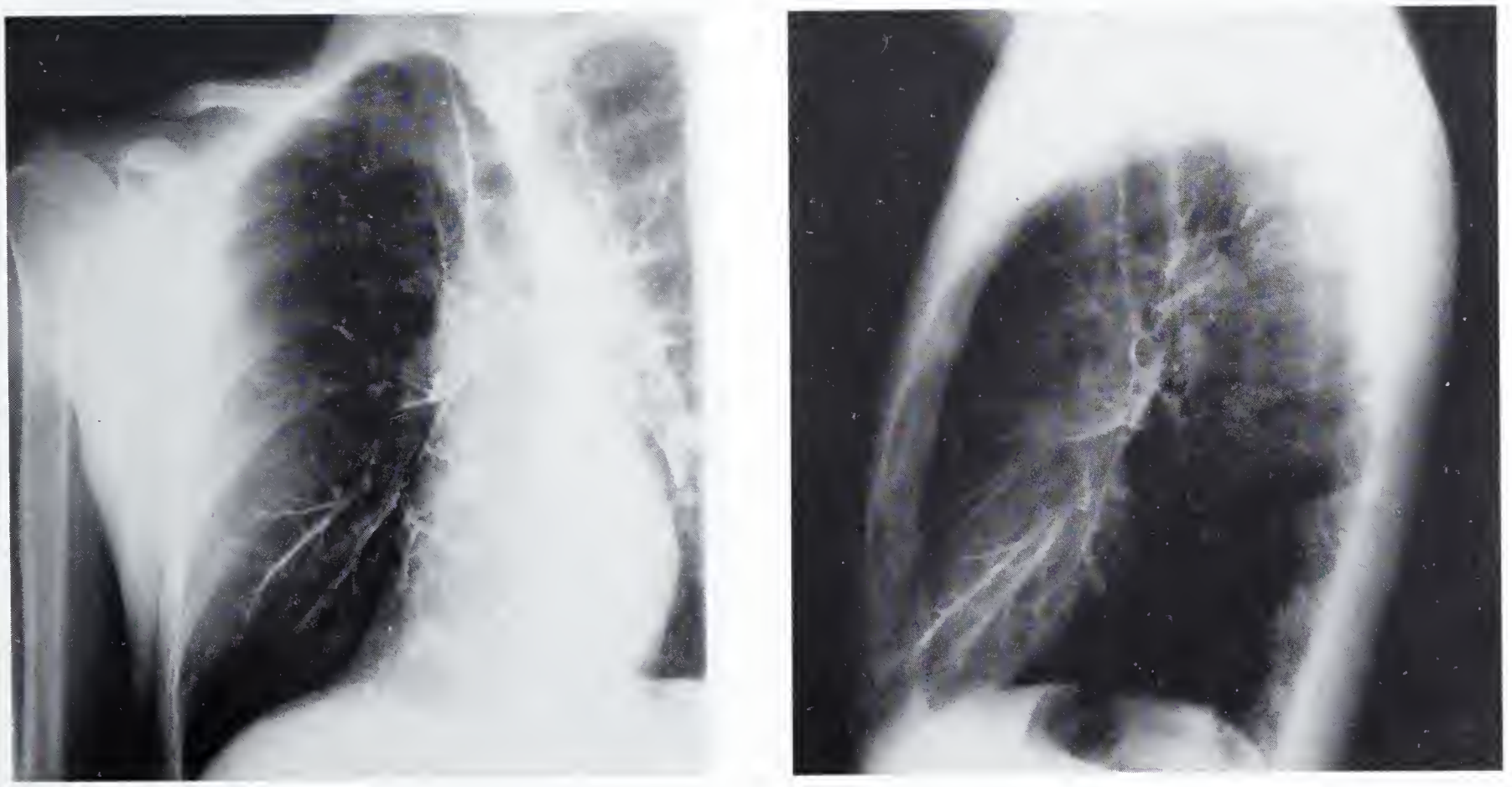


Figure (2a & b)
A bronchogram shows all the expected segments for a right lung. On the laterial view, however, the middle and lower lobe segmental bronchi are displaced anteriorly and there is a large segment of lung with no apparent bronchial supply.

Respirology Rounds — Answer

Diagnosis: *Bronchopulmonary Sequestration*

The diagnosis of Bronchopulmonary Sequestration was made on the basis of the following criteria: (i) the bronchogram demonstrated a portion of the right lung that was sequestered from the tracheobronchial tree, and (ii) an aortogram showed a *systemic* feeding artery to this region arising from the descending thoracic aorta (Fig. 3a & b). The venous phase of the aorogram showed a vein draining this area into the inferior pulmonary vein. The diagnosis of an intralobar bronchopulmonary sequestration was confirmed at thoracotomy (Fig. 4a & b).

Bronchopulmonary sequestration is a rare (about 600 reported cases) pulmonary disorder that affects both genders equally and has been described in all age groups. This disorder is defined by Pryce(1) as an area of nonfunctioning abnormal lung tissue, which has no connection with the tracheobronchial tree and receives its blood supply from a systemic artery. This anomaly is divided into an intralobar and extralobar form. The intralobar type is more common (>400 reported cases), with the abnormal lung tissue located within the visceral pleura of a pulmonary lobe. The extralobar type may appear similar to an accessory lobe because it sometimes has its own visceral pleural envelope. Generally, the diagnosis of intralobar vs. extralobar sequestration is made on the basis of the draining vein. If this vein drains into the systemic venous system, the sequestration is extralobar. If,

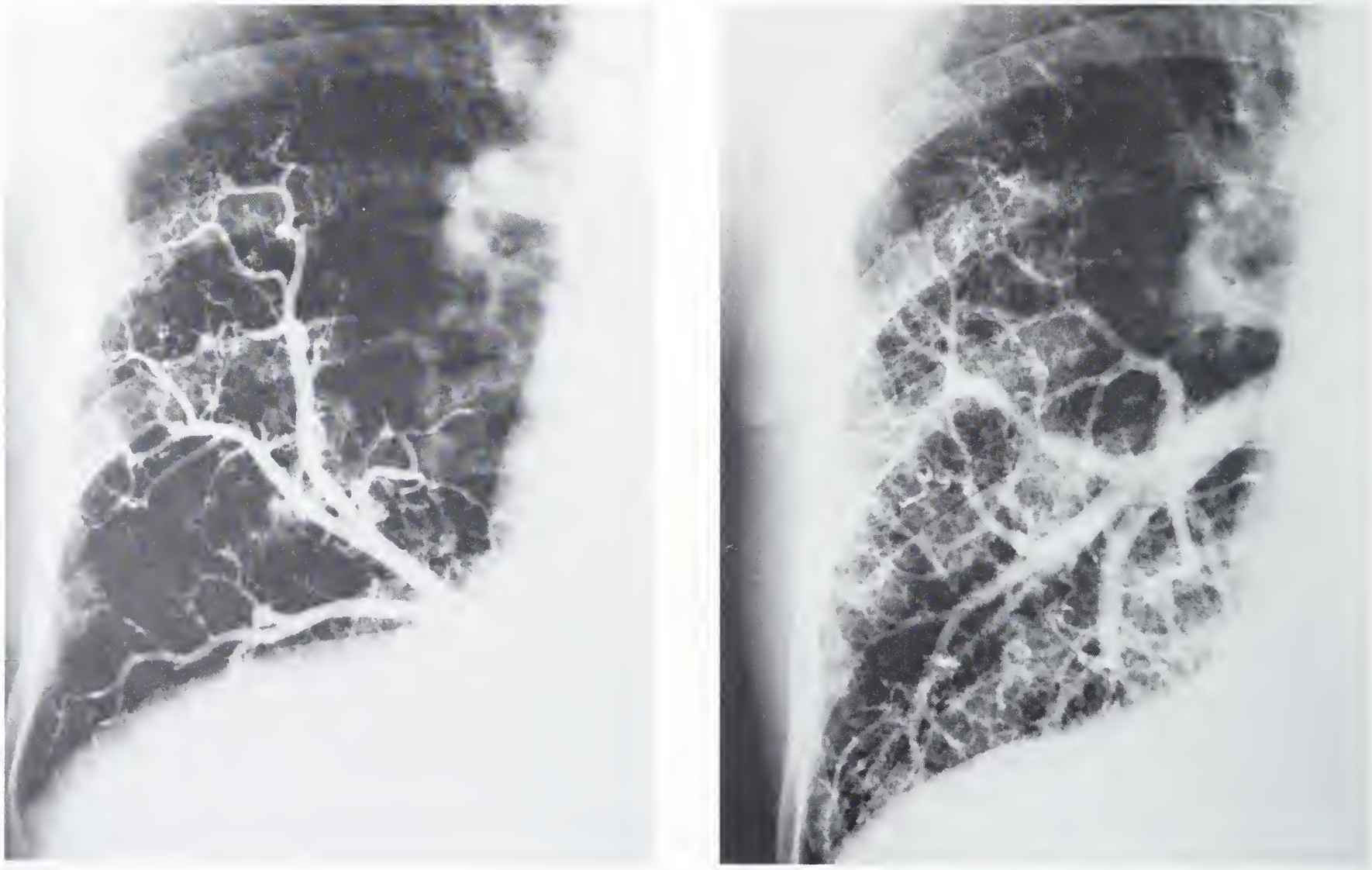


Figure (3a & b)

These films are taken from an arteriogram of the thoracic aorta. The arterial phase film (3a) shows a large systemic artery (see on other films to be arising directly from the aorta) supplying the area of abnormality on the chest film (c.f. Fig. 1a). A venous phase film (3b) shows contrast from this area draining into the pulmonary veins.

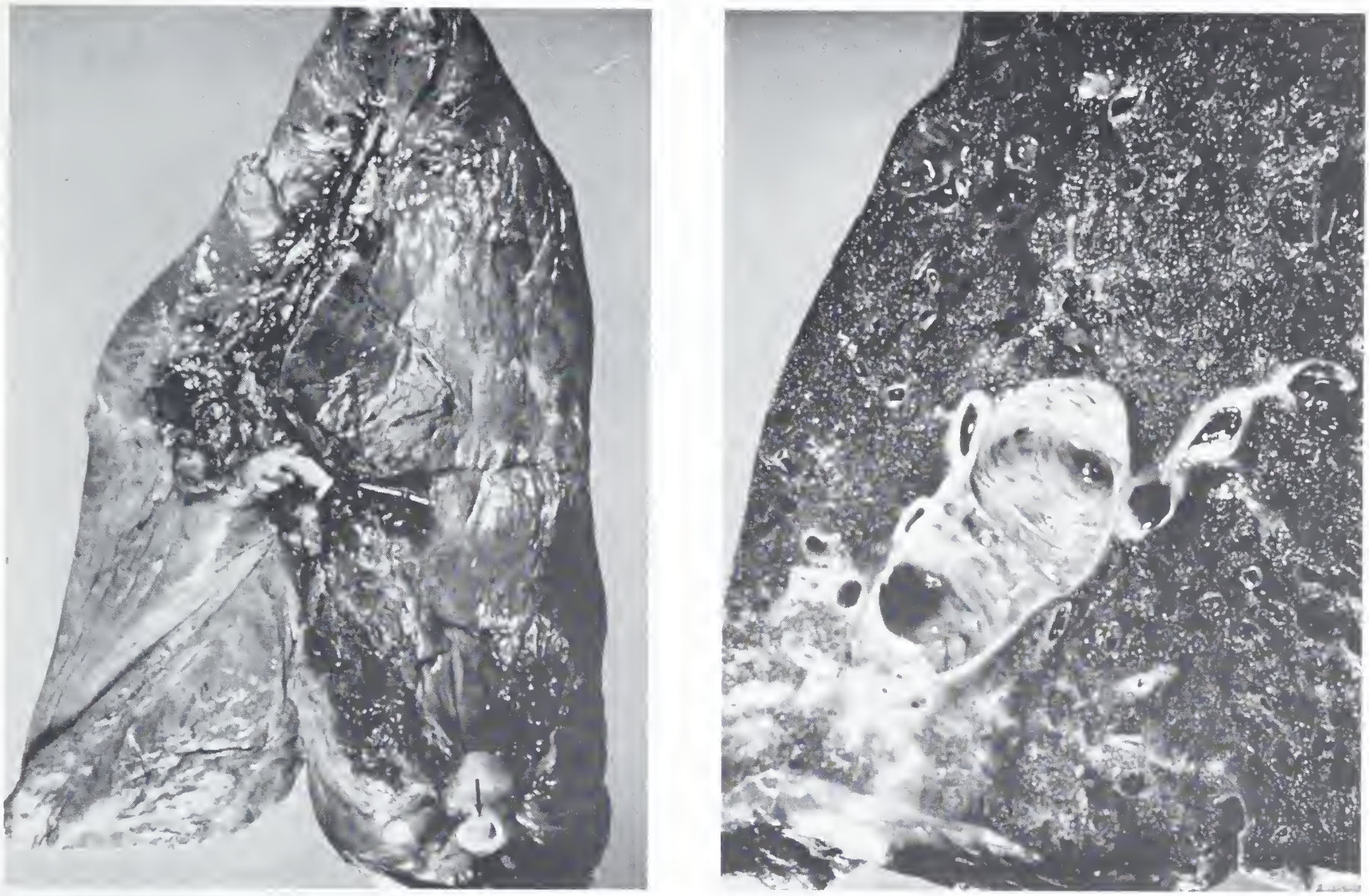


Figure (4a & b)

The gross pathology at the time of resection (4a) clearly shows the large systemic arterial branch posteriorly near the base of the right lower lobe (arrow). A magnified view (4b) demonstrates the cystic nature of the sequestration. Note also the patchy bronchopneumonia distal to the large cysts, suggesting endobronchial obstruction.

however, the vein drains into the pulmonary venous system, the sequestration is intralobar.

Bronchopulmonary sequestration is widely felt to be a congenital anomaly. The primary defect is believed to be due to insufficient pulmonary arterial vascularization during fetal lung development. The consequence is persistent systemic arterial vascularization after birth. The abnormally high pressure systemic blood supply leads to cystic degeneration and fibrosis of the sequestered lung tissue (2). However, recent autopsy studies by Stocker et al (3) led to the suggetion that the etiology of some of the intralobar anomalies may be acquired i.e. the consequence of poorly resolved bronchial obstruction in early childhood. The hypothesis is that bronchial obstruction leads to pulmonary vasoconstriction, compensatory systemic arterial vascularization by the pulmonary ligament arteries arising from the descending aorta, and cystic degeneration and fibrosis in the sequestered lung.

The key to making the diagnosis is to consider this entity in the following clinical scenario: (i) poorly resolving pneumonia in the lower lung zones, (ii) negative or confusing microbiology and cytology after numerous sampling procedures, (iii) evidence of cystic areas or cavities in the involved areas. In appropriate patients, the diagnosis can be established by an ipsilateral bronchogram and aortogram. A high-quality CT scan may be used in place of an aortogram for demonstrating the systemic feeding artery (4).

The optimal managemennt is unclear but the natural history of such a rare condition is very difficult to establish. Long-term followup (20 years) of asymptomatic patients has been reported. However, once infected, patients are at high risk of abscess formation in the sequestered lung, frequently complicated by empyema. Anecdotal reports in the literature and our own limited experience seem to support the following pragmatic approach: (i) observe the asymptomatic cases, (ii) identify the offending micro-organism(s) in the infected cases and treat with appropriate antibiotic(s), followed by surgical resection (ideally when the infection is quiescent).

References

1. Pryce DM. Lower Accessory pulmonary artery with intralobar sequestration of lung. *J. pathol Bacteriol* 1946; 58:457-467

2. O'Mara CS, Baker RR, Jevasingham K. Pulmonary sequestration. *Surg, Gyn & Obs.* 1978; 147: 609-616.

3. Stocker JT, Malczak, HT. A Study of pulmonary ligament arteries. Relationship to intralobar pulmonary sequestration. *Chest* 1985, 86: 611-615

4. Hochhauser L, Gray RR, St. Louis EL, Grossman H, Hutcheon MA, Hyland RH, Jones DP. Computed tomographic diagnosis of pulmonary sequestration. *Comput Radiol* 1983; 7:295-300.

The Effect of Propranolol and Epinephrine on Right Atrial Mechanical Function

Lloyd C. Semelhago, B.Sc., 8T8

Abstract

Propranolol and epinephrine are commonly used cardiac drugs with well recognized effects on the ventricles (of the heart). However, little is known of their influence on atrial function. This study examines the effects of the two drugs on the right atrium in 16 pigs (30-35 kg). Baseline function was assessed with an intracavitary compliant balloon at a paced heart rate in an isolated right atrial preparation. In group I (n = 8) 2 mg of propranolol and in group II (n = 8) epinephrine (0.1 mg/cc) was infused. At stable heart rates propranol decreased the heart rate to 90 bpm while epinephrine increased it to 180 bpm. Developed systolic pressure and dP/dt were decreased in group I ($P<0.05$) and increased in group II ($P<0.05$) after drug infusion. It was concluded that pharmacologic doses of propranolol and epinephrine have significant effects on atrial function in addition to their known effects on ventricular function.

Introduction

Since the turn of the century, numerous attempts have been made to determine the contribution of atrial systole to total cardiac output. These estimates range from 10-50%[1,2]. Left atrial stroke volume in a normal individual has been shown to be 24 ± 7.6 ml representing $37 \pm 13\%$ of left ventricular stroke volume. The mean fractional emptying of the atrium has been shown to be in the range of $65 \pm 9\%$ [3]. In normal individuals atrial pump function plays a minor role in total cardiac performance except during strenuous exercises[4]. In patients with compromised ventricular filling[5], the loss of atrial function may result in abrupt clinical deterioration. As expected from this, the contribution to left ventricular filling by atrial contraction is greater in patients who have suffered a recent myocardial infarction[6,7] or who are in heart failure. When atrial function is increased, more blood will be pumped into the ventricle and the pressure in the great veins will be lower at any given cardiac output[4].

The effects of beta blockers and inotropes on the ventricles are well known. We were interested in the effects of propranolol (Inderal®) and epinephrine on the mechanical function of the atrium. The right atrium was selected for study because of its easy accessibility and simple hemodynamic isolation. Propranolol, which acts by retarding nervous conduction and depressing the spontaneous depolarization of myocardium, is often used to control supraventricular tachyarrythmias such as paroxysmal atrial tachycardia, atrial flutter and atrial fibrillation. Similarly, we wish to examine how epinephrine, occasionally used to treat Low Output Syndrome (LOS) affects atrial function.

Materials and Methods

Sixteen pigs (30-35 kg) were anaesthetized with Nembutal (30 mg/kg) intraperitoneally and Pentothal (5 mg/kg) intravenously. A tracheostomy was performed and the animals were mechanically ventilated with 100% oxygen. A median sternotomy and pericardiotomy were performed and then the animals were heparinized (3 mg/kg). The left common carotid artery was cannulated with a #18 fluid-filled catheter for continuous monitoring of arterial blood pressure. The right common carotid artery was dissected free and ligated distally. A #14 cannula was then inserted via the carotid artery into the aortic arch. The azygous vein was ligated at its junction with the superior vena cava (SVC) and a #25 cannula was inserted into the SVC superior to the right atrium, and was later snared into position. A #30 cannula was advanced into the thoracic portion of the inferior vena cava which was then ligated proximally. Cardiopulmonary bypass was then instituted with a calibrated nonpulsatile Sarns roller pump and a Cobe membrane oxygenator, primed with 1500 ml of homologous pig blood. Mean perfusion pressure was maintained at 90 mm Hg at all times. The coronary sinus was incised near its junction with the right atrium to prevent return of venous blood to the chamber, and blood which drained into the pericardium was aspirated into the cardiotomy reservoir. Two unipolar leads were sutured (6-0 silk suture) to the right atrial appendage and the heart rate was monitored via limb leads.

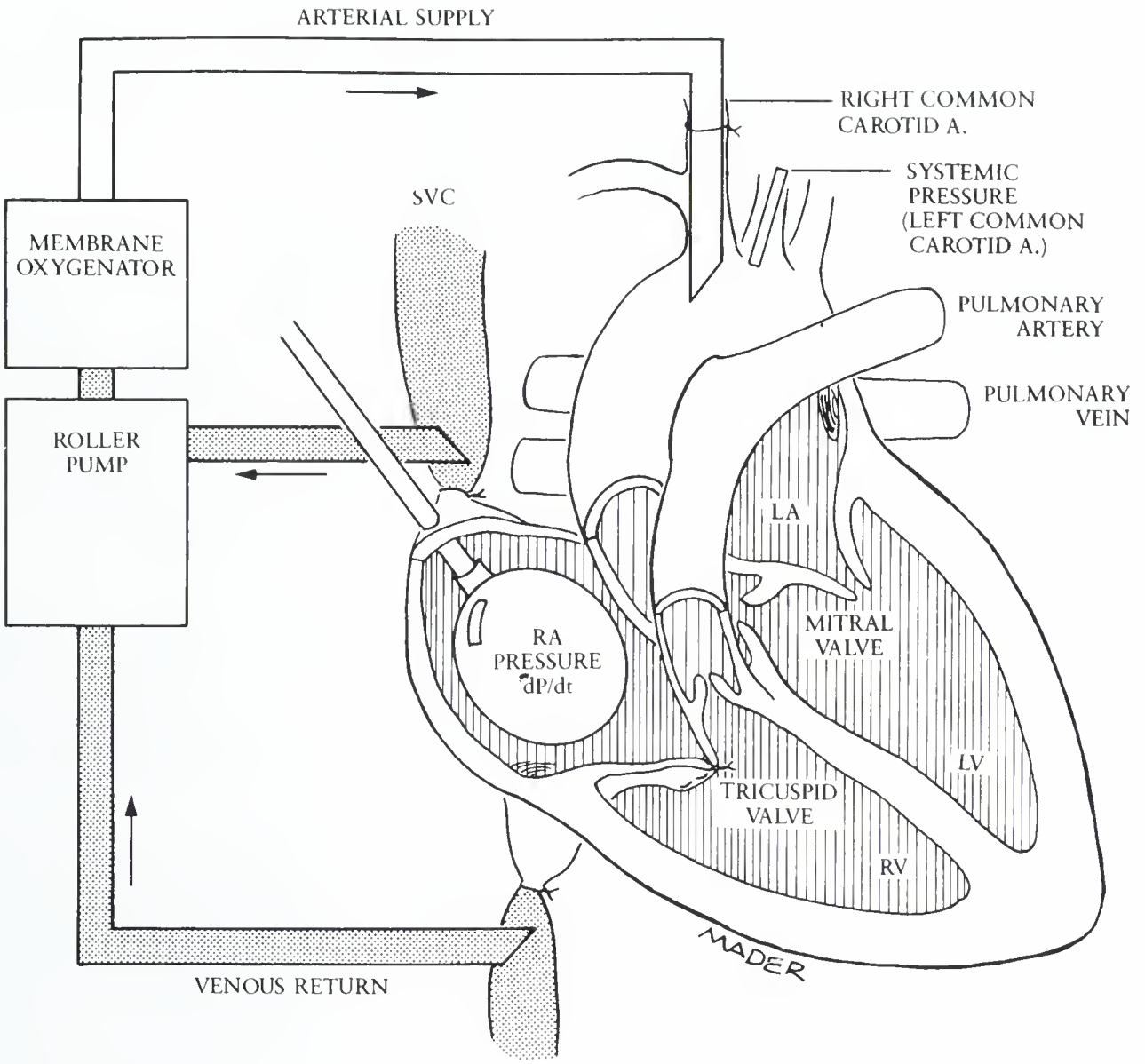


Diagram 1: Isolated right atrial preparation showing cardio-pulmonary bypass pump and oxygenator.

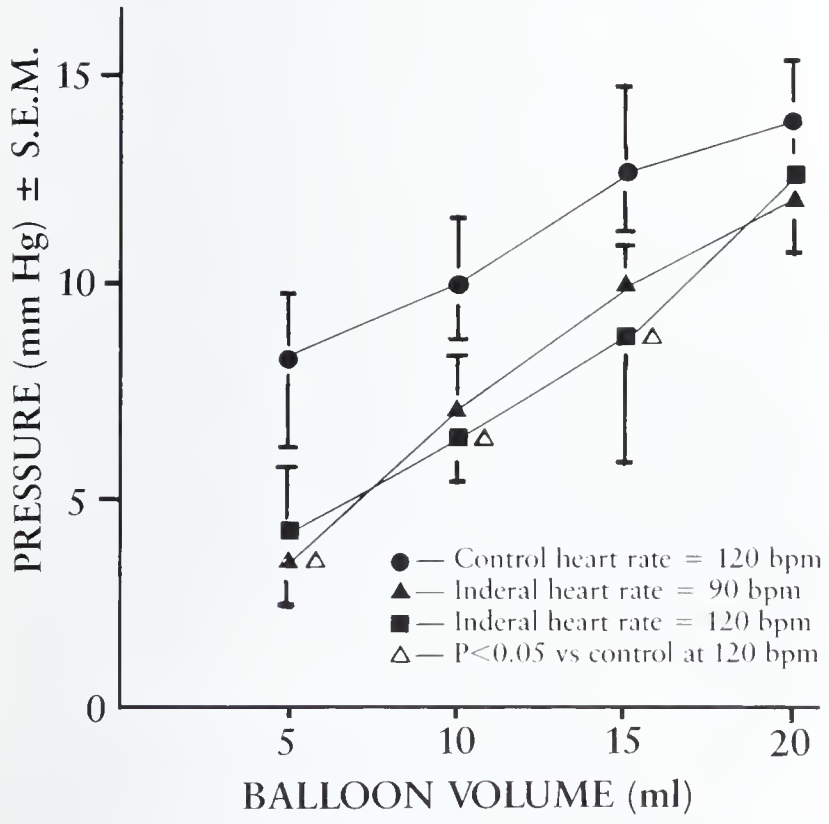


Figure 1: Atrial systolic pressure versus balloon volume after Inderal administration. Peak pressure generated is shown to be markedly lowered relative to the control value.

With the heart beating, a 3 cm ventriculotomy was performed at the apex of the right ventricle. A purse string suture was used to approximate the leaflets of the tricuspid valve to isolate the right atrium from the right ventricle. When the core temperature had stabilized at 37°C, a compliant balloon connected to a Statham P231D pressure transducer was inserted into the right atrium via the SVC proximal to where it had been snared. Sterile water was introduced into the balloon in 5 ml increments, to a maximum volume of 20 ml. The atrial pressure wave and its electronically differentiated first derivative (dP/dt) were recorded simultaneously on a Honeywell AR-6 recorder.

The animals were divided into two groups. In the first group, eight animals were given 2 mg of Inderal (propranolol) intravenously and right atrial function was recorded when the heart rate stabilized at 90 and 120 beats per minute (bpm) with or without the help of pacing. Each animal served as its own control in the absence of propranolol. The second group of eight animals were electronically paced at 180 bpm to serve as controls for the effect of heart rate on dP/dt and then pacing was discontinued so that sufficient epinephrine (0.1 mg/cc) could be infused to raise the heart rate to 180 bpm. In the absence of electronic and pharmacologic manipulation, each animal served as its own control at an intrinsic rate of 120 bpm.

The pH, arterial blood gases and electrolytes were maintained within normal physiological limits. Results were analyzed with the Students paired t-test and the data were reported as the mean ± the standard error of the mean. All animals were treated humanely according to National Academy of Science Guidelines.

Results

The results are summarized in Figures 1-6. Propranolol consistently produced a heart rate of 80-90 bpm and 115-120 bpm. Function was assessed at heart rates of 90 and 120 bpm. At both of these rates, there was a significant decrease in the systolic pressure and the dP/dt (Figures 1 and 2) at the $P<0.05$ level of probability. A minute increase in the diastolic pressure (Figure 3) for heart rates of 90 to 120 bpm relative to the control values was noted, but this was not significant at the $P<0.05$ level. No change was observed in the compliance ($\triangle V/\triangle P$) of the chamber myocardium for the balloon volume range of 5-20 ml (Figure 3).

Upon infusion of epinephrine, there was a significant increase ($P<0.05$) in the systolic pressure for 10, 15 and

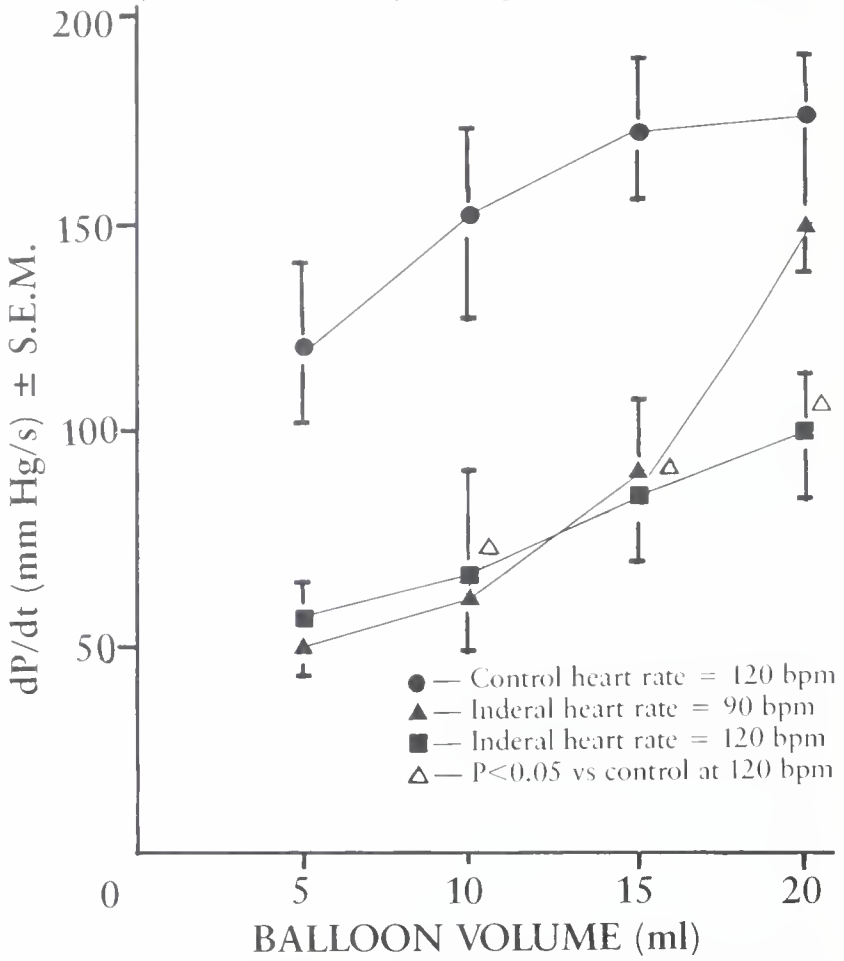


Figure 2: dP/dt versus balloon volume after Inderal administration. The rate of change of atrial chamber pressure is shown to be lowered at heart rates of 90 and 120 bpm.

20 ml of balloon volume as compared to the control in which the heart rate was at its intrinsic value of 120 bpm. Comparison with the control in which the heart was electronically paced at 180 bpm yielded a significant increase ($P<0.05$) in atrial systolic pressure for 5, 10, 15 and 20 ml of balloon volume (Figure 4). No difference was detected between the systolic pressures generated when the controls were compared to each other in the absence of epinephrine at 120 and 180 bpm. The rate of change of chamber pressure was significantly elevated relative to the controls at 120 and 180 bpm for only 10, 15 and 20 ml of balloon volume (Figure 5). No significant changes in diastolic pressure and hence compliance were observed following administration of epinephrine, and pacing the heart at 180 bpm also did not affect it (Figure 6).

Discussion

Isolated atrial mechanical function is difficult to mea-

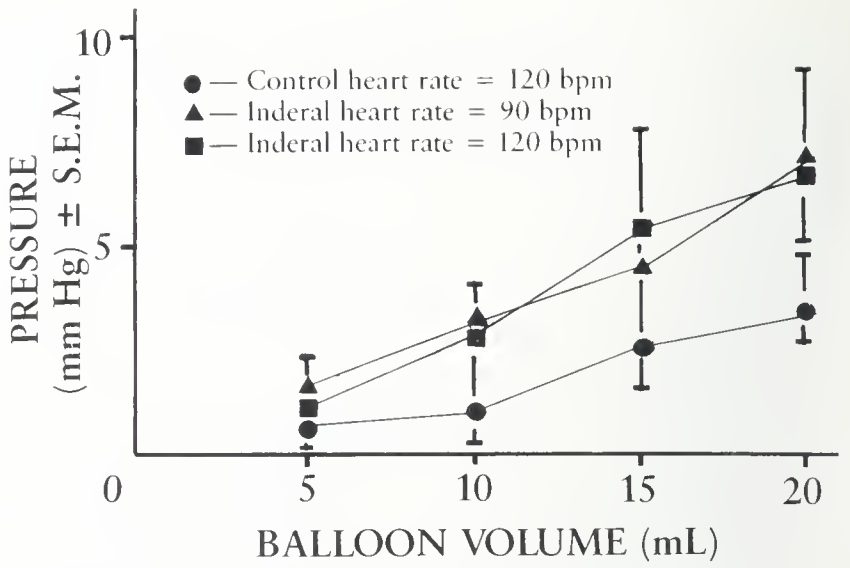


Figure 3: Right atrial diastolic pressure versus balloon volume after Inderal administration. Peak diastolic pressure is not significantly affected by the beta-blocker.

sure accurately. In this laboratory, an isolated right atrial model has been developed using a compliant intracavitary balloon to assess contractility of the myocardium. The atria serve three major hemodynamic functions: as a conduit between the great veins and the ventricles, as a reservoir during ventricular contraction and as a booster pump. As a reservoir, the atrium ensures that blood flowing from the venous system is available in adequate quantities to fill the ventricle during early diastole. In animals at rest, this function is unimpaired until half of the atrial capacity is lost[8]. The pump and reservoir functions of the atria are difficult to distinguish experimentally. As in the ventricle, atrial pump function is controlled by preload, afterload and contractility[9,10], in a manner similar to the Frank-Starling relationship. In fact, the atria are capable of generating pressures similar to the ventricles when

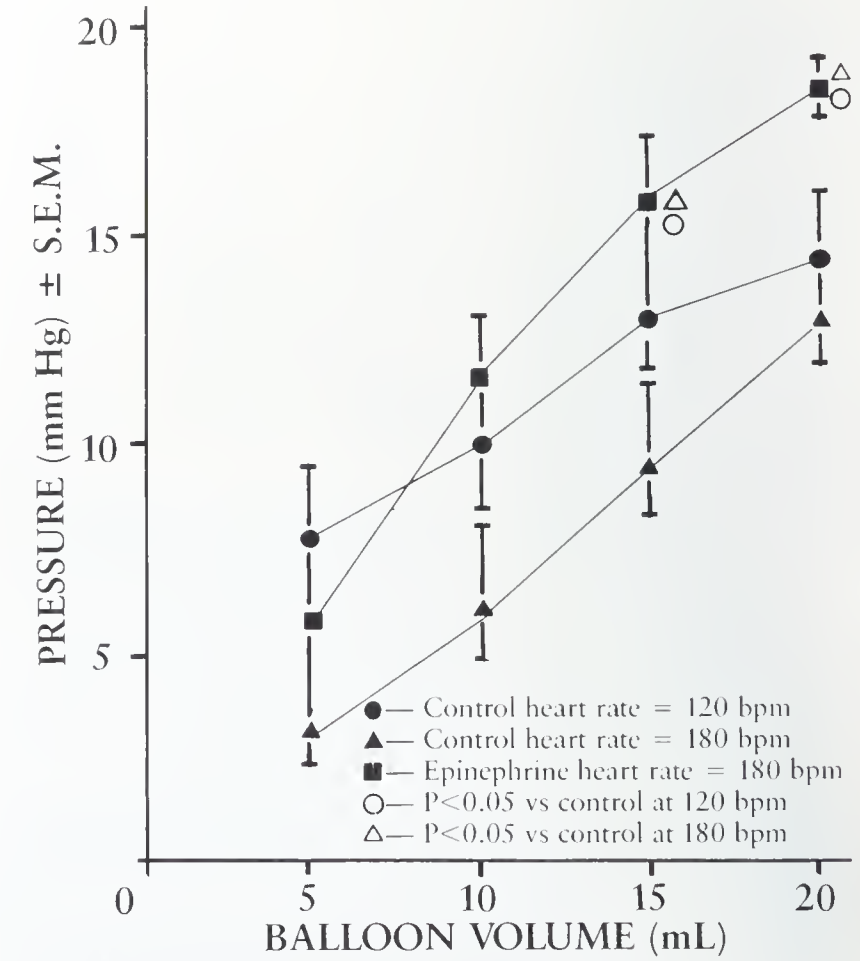


Figure 4: Right atrial systolic pressure versus balloon volume after epinephrine administration. Peak pressure generated is shown to be significandy elevated when compared to both controls at 120 and 180 bpm.

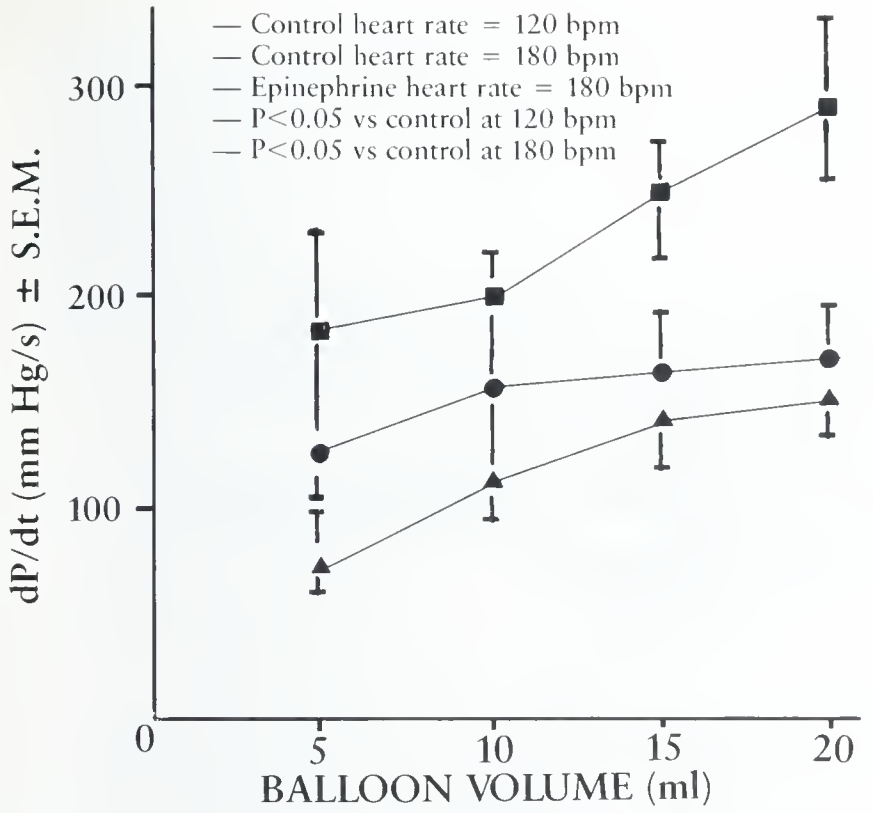


Figure 5: dP/dt versus balloon volume after epinephrine administration. The rate of change of atrial chamber pressure is shown to be significantly increased when compared to controls at 120 and 180 bpm.

corrected for differences in muscle mass[9]. When the volume of the atrium is increased, there is an initial increase in atrial contractile shortening. However, as atrial distension continues, the magnitude of atrial shortening levels off as depicted by both of the control plots of dP/dt (Figures 2 and 5). Thus pump function may be impaired by volume overload, but reservoir and conduit functions remain intact.

Atrial contractility, measured by the rate of change of chamber pressure (dP/dt) was shown to be depressed by propranol to the same extent regardless of the heart rate. While the peak systolic pressure was markedly depressed, the peak diastolic pressure was not significantly affected. The diastolic pressure curve, a reflection of compliance, shows no major difference due to propranolol. These results have clinical implications since propranolol is occasionally used to prevent and treat the supraventricular tachyarrhythmias (SVTs) that commonly follow cardiac surgery. Propranolol in these situations may further depress the low output caused by such arrhythmias by further lowering ventricular end-diastolic pressure. Other clinical conditions that may affect atrial mechanical function include ischemic injury to the myocardium as a result of inadequate preservation during cardioplegic arrest in surgery, and also damage to conduction pathways of the atria.

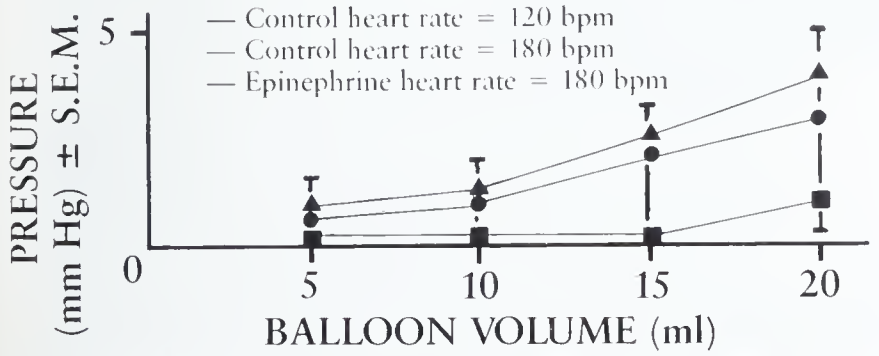


Figure 6: Right atrial diastolic pressure versus balloon volume after epinephrine administration. Peak diastolic pressure is not significantly affected by the inotrope.

atria.

The effect of epinephrine on atrial function was similar to its effect on the ventricles in terms of increases in contractility and rate. This was achieved by directly altering the permeability of the myocardial sarcolemma leading to a faster influx of Na^+ (and Ca^{2+}), as well as increasing the rate of discharge of pacemaker cells in the sino-atrial node[11]. A practical application of epinephrine would be in the treatment of low output syndrome where stronger atrial contraction will increase ventricular performance by raising the preload. The methodology used in this study, although common for the assessment of left ventricular function, has only recently been used for evaluating atrial function[12]. The isolated right atrial model permits assessment of changes in the function of the right atrium independent of the other chambers. The right atrium was selected over the left due to its greater accessibility and ease of isolation. To avoid injury to this chamber venous cannulation was conducted away from the right atrium. Also, ventriculotomy was performed at the apex of the right ventricle to avoid interference with the perfusion of the atrium.

Summary

This study evaluated the relevance of modulating atrial function in order to control cardiac output. The results clearly showed that propranolol decreased the mechanical function of the atria, while epinephrine increased it. The results also suggested that greater emphasis must be placed on the pharmacological treatment of the atria, which are too often disregarded when ventricular therapy is being administered.

Acknowledgements

The author is indebted to Dr. C. Peniston, Dr. H. El-Dalati, Mr. K. Jabr and Dr. T. Salerno of the Division of Cardiovascular Surgery, St. Michael's Hospital, Toronto. Special thanks also to the Medical Research Council for the summer scholarship that enabled this project to be carried out.

References

1. Gessell, R.A. (1916): Cardiodynamics in heart block as effected by auricular systole, auricular fibrillation, and stimulation of the vagus nerve. *Am. J. Physiol.* 40: 267-313.
2. Wiggers, C.S., and Katz, L.M. (1922): The contour of the ventricular volume curves under different conditions. *Am. J. Physiol.* 58: 439.
3. Gutman, J., Wong, Y., Wahr, D., Schiller, N.B. (1983): Normal left atrial function determined by two-dimensional echocardiography. *Am. J. Card* 51: 336-340.
4. Hurst, J.W.: The Heart. W.B. Saunders. 4th Edition, 1978.
5. Guyton, R., Andrews, M., Hickey, P., *et al* (1976): The contribution of atrial contraction to right heart function before and after right ventriculotomy. *J. Thorac. Cardiovasc. Surg.* 71: 1-10.
6. Matsuda, Y., Toma, Y., Ogawa, H., Matsuzaki, M., Katayama, K., Fuji, T., Yoshino, E., Maritani, H., Kumada, T., Kusukawa, R. (1983): Importance of left atrial function in patients with myocardial infarction. *Circulation* 67: 566-571.
7. Rahimtoola, S., Ehseni, A., Sinno, M., Loeb, H.S., Rosen, K.M., Gunnar, R.M. (1975): Left atrial transport function in myocardial infarction. Importance of its booster pump function. *Am. J. Med.* 59: 686-694.
8. Trusler, G., Bull, R., Hoeksema, T. (1963): The effect on cardiac output of a reduction in atrial volume. *J. Thorac. Cardiovasc. Surg.* 46: 109-116.
9. Williams, J., Sonnenblick, E., and Braunwald, E. (1965): Determinants of atrial contractile force in the intact heart. *Am. J. Physiol.* 209: 1061-1068.
10. Payne, R., Stone H., and Engelkin, E. (1971): Atrial function during volume loading. *J. Appl. Physiol.* 31: 326-331.
11. Kalant, H., Roschlau, W.H.E., Sellers, E.M. *Principles of Medical Pharmacology* 4th Edn. 1985. University of Toronto Press, Toronto.
12. Spence, P.A., Peniston, C.M., Weisel, R.D., Jabr, A.K., Yap, V., Salerno, T.A. 1985: Is Atrial Function Affected by Conventional Cardioplegic Arrest? *J. Surg. Res.* 38: 509-514.

Biomechanical Assessment of Joint Resurfacing: A Comparison of the Effects of Immobilization, Intermittent Active Motion and Continuous Passive Motion

Sherif P. Nessim, B.A.Sc., 8T8 and Robert B. Salter, M.D., F.R.C.S.(C), F.A.C.S. *

Abstract

A rectangular graft of autogenous tibial periosteum was sutured (with its cambium layer facing into the joint) onto the base of a 5×10 mm full-thickness defect in the patellar groove of each of 23 adolescent rabbits. The rabbits were managed post-operatively for four weeks by either: 1) Continuous Passive Motion (CPM, 8 rabbits), 2) Immobilization (IMM, 8 rabbits) or 3) Intermittent Active Motion (IAM, 7 rabbits). The femora were excised and the mechanical characteristics of the grafted areas were compared with those of normal cartilage using an indentation test for cyclic load-deflection response, stress relaxation, and viscoelastic recovery. Previous experimental investigations by Salter[1] and co-workers have revealed that in four weeks of post-operative treatment with CPM new tissue was produced that was similar to hyaline articular cartilage in terms of its gross appearance, histology, histochemistry, and biochemistry ("neochondrogensis"). This investigation demonstrates that Continuous Passive Motion and Immobilization both result in tissue that is biomechanically superior to that resulting from Intermittent Active Motion.

Introduction

The resurfacing of destroyed joints by the interposition of various biological materials between the denuded ends of articular bones has been attempted for more than a century by orthopaedic surgeons. Much work has been put into the resurfacing of damaged joints in both experimental animals[2,3] and in humans.[4,5] However, after 8-12 months of normal function the newly formed tissue tends to degenerate[6] thus negating any short-term benefits.

As a viable alternative, periosteum has been considered as a means of resurfacing the damaged joints. Its deep layer, the cambium layer, is composed of relatively undifferentiated dual potential mesenchymal cells.[7,8] The dual potential of periosteum indicates its ability to produce both cartilage and bone. Rubak et al.[9] have studied the chondrogenic potential of peristeal grafts and further stated the importance of joint movement to the resurfacing process.

Salter's group studied the concept of periosteal grafting as a means of resurfacing the damaged joint and hypothesized the added advantage of Continuous Passive Motion (CPM) to the healing process.[10,11] Basic research has led Salter to conclude that CPM is well tolerated, seems to be painless, and stimulates and improves the healing and regeneratioin of articular tissues.[10,11] A recent study[12] has shown that when a joint is resurfaced by periosteum and managed under the influence of CPM for four weeks post-operatively, the regenerated cartilage resembles hyaline cartilage macroscopically, histologically, histochemically, and biochemically. However, to date, the biomechanics of the regenerated cartilage have not been tested.

The results from previous work have shown that CPM is a clinically viable means of treating damaged synovial joints via biological resurfacing. Such biological resurfacing would be a valuable alternative to joint excision and prosthetic joint replacement, especially in the young patients. Biomechanical testing of the resurfaced joint is necessary to confirm the therapeutic advantages of periosteal grafting with post-operative CPM treatment.

In this study, periosteal grafts were performed as described by Salter et al.[10], and the rabbits were managed post-operatively for four weeks with one of either CPM, cast (Immobilization), or cage (Intermittent Active Motion). This investigation demonstrates that CPM and Immobilization both result in tissue which is biomechanically superior to that produced with Intermittent Active Motion.

**Division of Orthopaedic Surgery and the Research Institute, Hospital for Sick Children, Toronto.*

Materials and Methods

The general operative and post-operative methods have been thoroughly outlined in a previous work.[12] A total of 23 male adolescent rabbits (weighing between 2.0-2.6 kg each) were purchased from one supplier, fed the same diet (Purina rabbit pellets and water and libitum, with cabbage, lettuce or carrots once a day) and housed individually under similar conditions in standard cages ($60 \times 45 \times 32$ cm).

In the operative procedure[12], the patella was dislocated laterally and a full-thickness transverse defect, measuring 5mm longitudinally and traversing the entire width of the patellar groove, was created using a coping saw and a rongeur. The base of the defect was flat and below the level of the cortical subchondral bone plate (Figure 1).

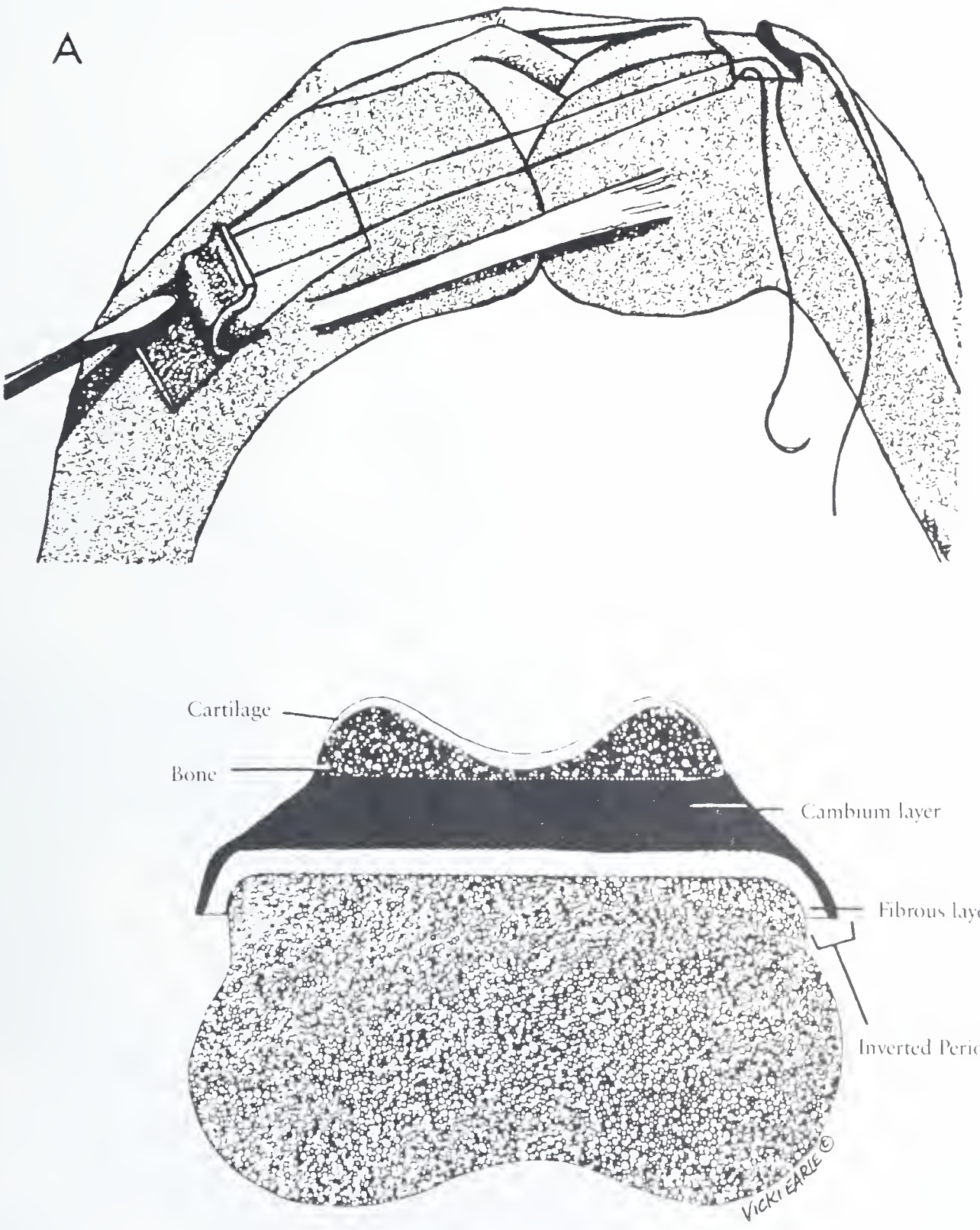


Figure 1. A) The Surgical procedure used to resurface the joint.
B) Tranverse section through the periosteal gratt in the defect.
Used with permission; O'Driscoll (1).

Each animal was assigned to one of three general treatment groups according to the type of post-operative treatment to be used: IMM — immobilization in a long-leg cast, with the knee and ankle flexed such that the rabbit could walk and hop as normally as possible; IAM — Intermittent Active Motion in a cage in which the rabbit was allowed to move freely; and CPM — Continuous Passive Motion. Treatment was instituted while each animal was still under general anesthesia.

Continuous Passive Motion

A specially constructed appartus was used to provide Continuous Passive Motion (Figure 2). This apparatus has been described in previous publications.[12,13,14] The appartus was calibrated so that the knees of the rabbit moved through a range of motion of 70°, from 40° to 110° of flexion. A rate of one cycle every 45 seconds was used since it had been concluded from early investigation of CPM that slower rates did not provide as much stimulation for cartilage regeneration, and faster rates were not tolerated as well by the rabbits.[12] In front of each rabbit was a wooden structure that provided support for its forelimbs and contained bowls for food and water. The animals ate and drank well and appeared to remain as healthy as those that had been placed in cages.

Of the 23 rabbits used in this study four died post-operatively of pasteurella pneumonia leaving 19 for the analysis (CPM-6, IAM-6, IMM-7).

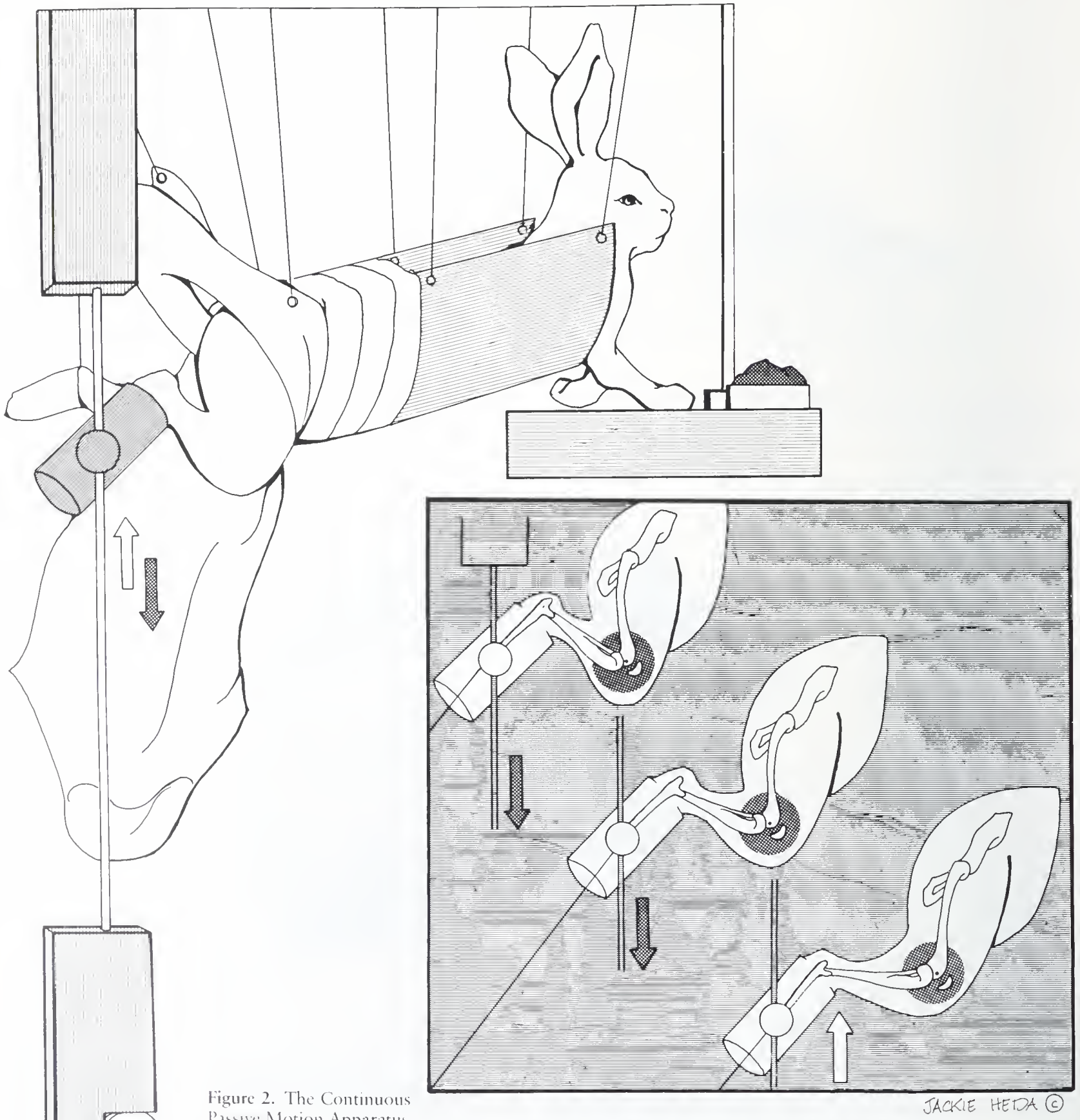


Figure 2. The Continuous Passive Motion Apparatus. Used with permission; O'Driscoll (1).

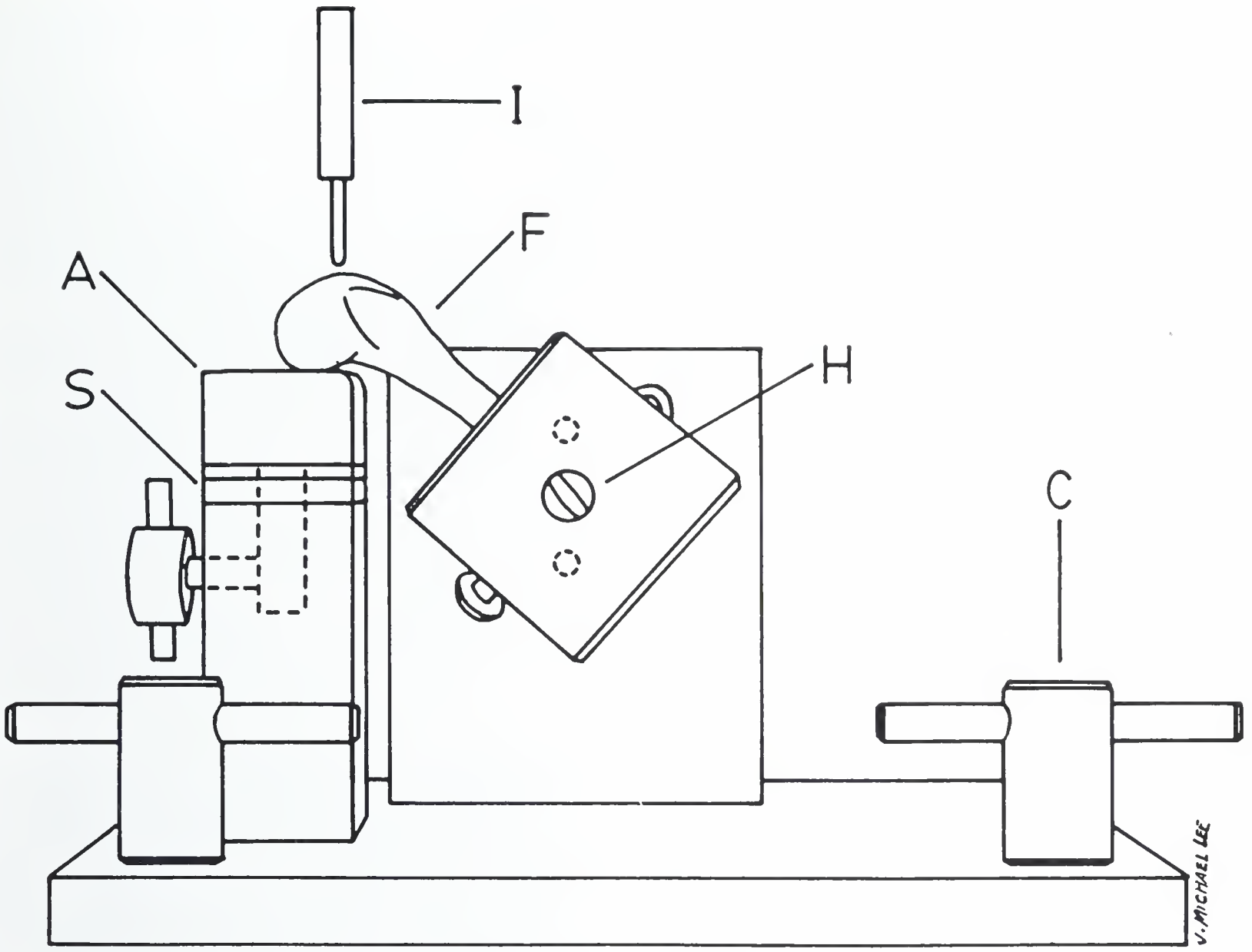


Figure 3. The Apparatus used to test the biomechanical properties of the regenerated articular surface. Refer to text for full description. Used with permission; Lee et al (19).

Four weeks after surgery, the rabbits were sacrificed by an overdose of intravenous Sodium Pentobarbital (1 ml of a 240 mg/ml solution). The six contralateral, non-operated femora of the IAM animals (who ambulated in the most nearly normal fashion) were also excised to act as controls for the biomechanical testing.

Biomechanical Testing

Prior to testing of the regenerated tissue, the femora were carefully cleaned of adherent connective tissue and the cartilage was scraped from the posterior aspects of the femoral condyles to expose the subchondral compact bone. The femora were then osteotomized at the proximal metaphysis leaving the knee joint and the diaphysis intact. The femur was then mounted into a specially designed stainless steel device for cartilage indentation testing (Figure 3). The apparatus consisted of a holder (H) through which the femur (F) was inserted and clamped with three sharp-ended set screws. These were placed 120° apart around its cross-section and anchored into the diaphyseal cortical bone. The device then allowed the position of the femur to be adjusted both laterally and rotationally so that its condyles (with cartilage removed) rested firmly on a vertically adjustable anvil (A). This was achieved by rotating the femur in the holder, moving the holder to another axis hole (dotted circles above and below the central set screws), and changing spacers (S) under the anvil. The removal of the condylar cartilage ensured that the compressional properties of this tissue did not influence the subsequent mechanical testing of the newly formed tissue in the pastellar groove; the interface between the femur and the anvil was of cortical bone to steel without intervening soft tissue. The flexibility in positioning the femur was important in ultimately ensuring that the cartilage indentor (I) was normal to the surface being tested.

For the biomechanical testing an indentor (I) made of 316L stainless steel, measuring 1 mm in diameter both at the shaft and at its rounded end, was used. It was attached to a 50 kg tension/compression load cell in the fixed beam of the Instron machine. Once the bone was positioned in the holding device the entire bone and holding device assembly was clamped into a plexiglass tissue bath using quick-release stainless steel bolts and wing screws (C). The bath was then placed on the moving beam of an Instron universal testing machine, aligned with the indentor and attached with C-clamps. During the entire dissection and mounting procedure the bone was kept wet with Hanks Solution. Once the mounting was complete, the bath was filled with Hanks Solution, (41°C); the actual tests were performed with the temperature between

38.5°C and 39.5°C (body temperature of the rabbit being 39°C). Hanks Solution (pH = 7.4, 310 mOs) was prepared so that the solution would be isotonic with respect to the cartilage.

A constant load rate of 0.5 mm per minute and a maximum load of 100 grams were used. The maximum load was set so that irreversible damage to the cartilage could be avoided, thus allowing more than one trial in each part of the cartilage. The testing procedure yielded a chart for each trial showing the load, in grams, versus the indentation, or deflection, of the indentor into the cartilage in micrometers.

There were three separate procedures carried out on the cartilage. The first consisted of an indentation test whereby the indentor was applied to the cartilage, at a constant load rate of 0.5 mm/min, until a load of 100 grams was being exerted, at which time the indentation was stopped. The second test was a continuation of the first whereby the relaxation of the cartilage was observed by leaving the indentor in the cartilage at the maximum load and then observing the load decay over 100 seconds. The last test was carried out by removing the load from the indentor then measuring the increase in the load as the cartilage recovered from its deformation and exerted a back pressure on the indentor.

During the indentation testing, the cartilage was divided into proximal and distal halves. Two indentations were put in each part so that a series of charts were produced for each leg labelled as: distal-1, distal-2, proximal-1, and proximal-2. The four trials yielded results that virtually overlapped one another, hence, the mean of these four measurements for each rabbit was used for the statistical comparison of the post-operative treatments.

In assessing the signifance of the results a one-way analysis of variance was carried out. An F-test was used to determine whether there was any difference between the three post-operative procedures, then a modified t-test was used to determine pairwise differences.

Results

The gross appearances of the periosteal graft groups (CPM, IMM, IAM) at four weeks were consistent with those of O'Driscoll.[10] The greatest variablitiy in appearance was in the IAM animals, and this was reflected in the indentation results below; the greatest scatter in the data was observed with this group. The CPM group showed the most uniform gross appearance with a smooth, translucent surface; nonetheless, as with the other groups, the margins of the graft were easily discernable from the surrounding normal cartilage.

The mechanical testing regimen which was employed was a continuous sequence of loading, relaxation, unloading, and recovery. This was then repeated. The test results for loading, relaxation, and recovery are shown separately in Figures 4, 5, and 6 respectively. In Figure 4, the load versus deflection results are shown as load, in grams, versus mean deflection, in microns, for each treatment group. As expected, all the curves were concave upward, consistent with the behaviour of soft connective tissue in compression. Under any given load, the normal (control) cartilage deformed significantly less than any of the treatment groups ($p<0.05$) and showed very little scatter. The CPM and IMM groups were inseparable, and both were significantly less deformable than the IAM group ($p<0.05$). The loading stiffnesses of the tissues (the slopes of the load versus deflection curves under a given load) showed the same relationships. The control group was stiffer than the CPM or IMM group, and the IAM group was the least stiff. No treatment group produced regenerated tissue with a load versus deflection response similar to that of normal cartilage, however, CPM and IMM treatments were significantly better than IAM in this respect.

Since each treatment group displayed different load-deflection responses, the loading time for each group under constant deflection was different. The deflection rate of 0.5 mm/min (500 microns/min) was chosen as the

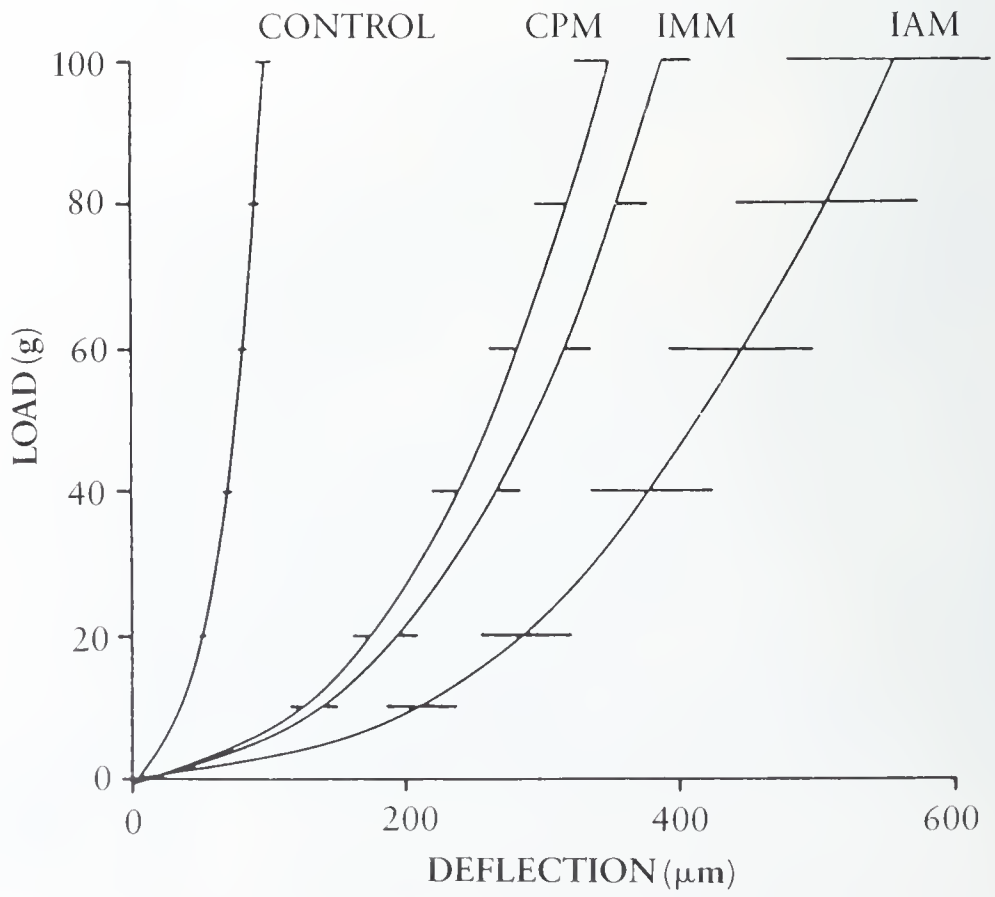


Figure 4. Load vs Deflection for Normal Cartilage as compared to regenerated cartilage under the influence of CPM, IMM and IAM post operatively (CPM, n = 6; IAM, n = 6; IMM, n = 7. Normal is statistically different from CPM, IAM and IMM and CPM and IMM are both statistically different from IAM with $P<0.05$). Data presented as the mean ± the standard error of the mean.

Used with permission; Lee et al (19).

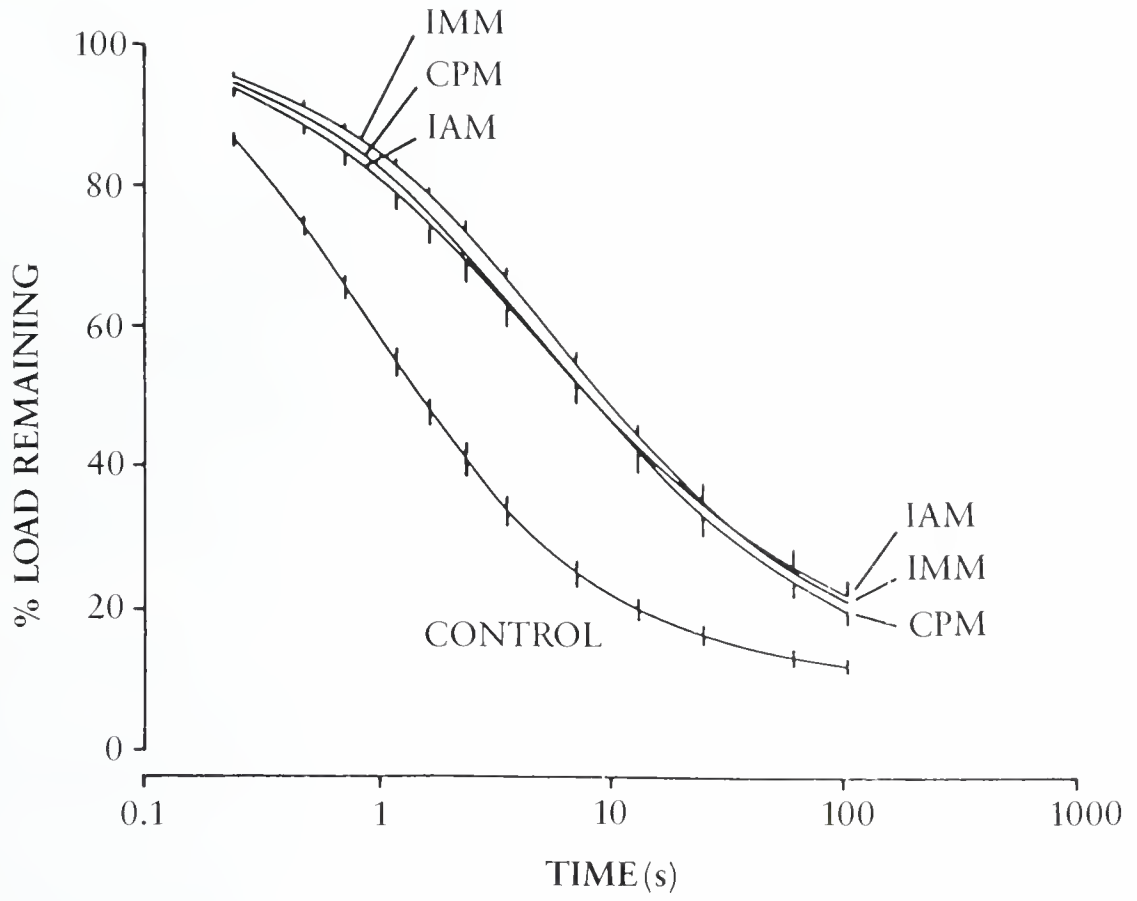


Figure 5. Percentage Load remaining vs Log of Time for Normal Cartilage as compared to regenerated cartilage under the influence of CPM, IMM, and IAM post-operatively (CPM, n = 6; IAM, n = 6; IMM, n = 7. Normal is statistically different from the rest with $P<0.005$). Data presented as the mean ± the standard error of the mean.
Used with permission; Lee et al (19).

fastest well-controlled rate on the testing machine. For the stiffness samples: the normal (control) cartilage, the deflection of 100 microns under 100 grams of load occurred in 12 seconds. For the CPM and IMM groups, loading to 100 grams required a deflection of 300 microns and 36 seconds. For the IAM group, loading to 100 grams required a deflection of 500 microns and 60 seconds. The relaxation data are likely affected to some degree by the required loading time.

In the relaxation experiments, the samples were loaded to 100 grams and the deformation held while the load decayed away. In Figure 5, the load relaxation data for each treatment group is presented as the mean percentage of the original load (100 grams) remaining at a given time in seconds after the maximum load was achieved. In keeping with engineering stress relaxation analysis, the decay in load is plotted against the logarithm (base 10) of time. Plotting of relaxation data against time on a linear

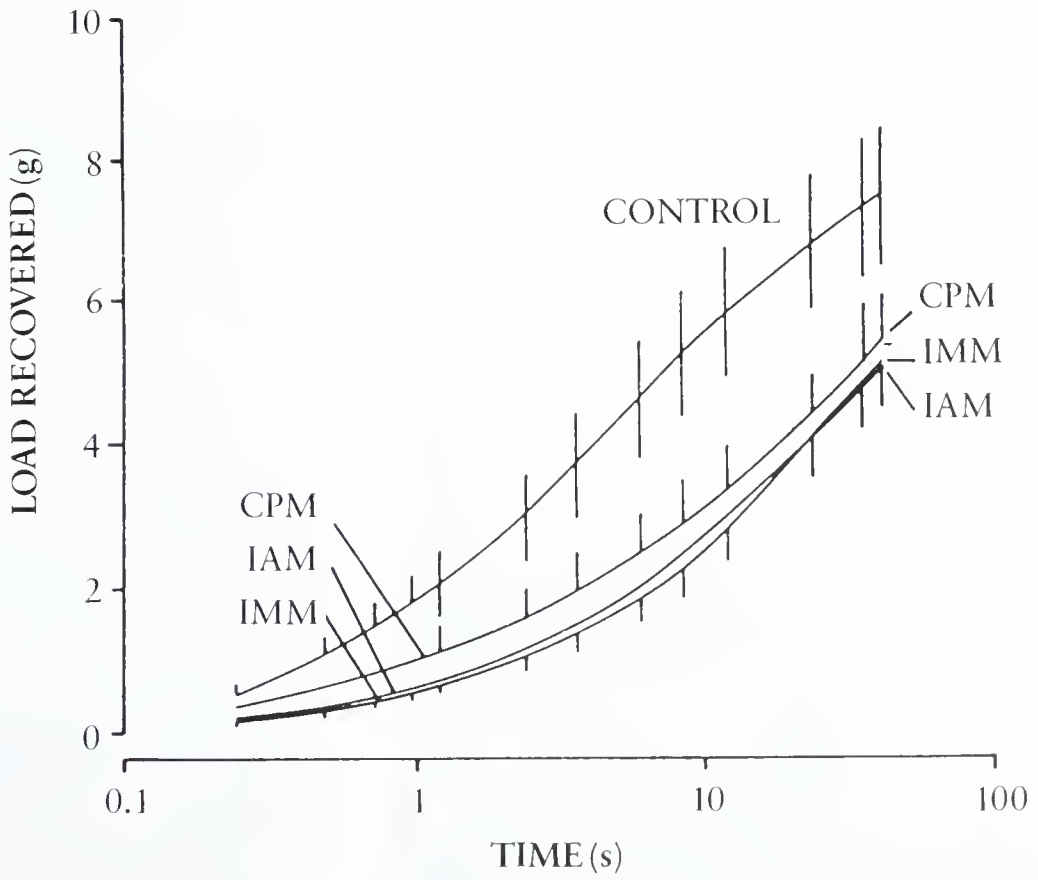


Figure 6. Load Recovery vs Log of Time for Normal Cartilage as compared to regenerated cartilage under the influence of CPM, IMM, and IAM post-operatively (CPM, n = 6; IAM, n = 6; IMM, n = 7. Normal is Statistically different from the rest with $P<0.05$). Data presented as the mean ± the standard error of the mean.
Used with permission; Lee et al (19).

scale can give the false appearance of an asymptotic limit when, in fact, slow relaxation is continuing. All samples showed a sigmoidal curve. The control cartilage showed significantly more stress relaxation than any of the treatment group ($p<0.005$). The three treatment groups could not be separated statistically. Thus, in this study, no treatment group produced regenerated tissue similar in relaxation response to normal cartilage.

Figure 6 shows the recovery response of each treatment group as the mean recovered load, in grams, versus time, in seconds. This was the load on the indentor a short time after it was raised, so as to initially exert no load on the cartilage. There was still a slight indentation in the tissue, but as this recovered, an increased force was observed at the indentor. The recovery of the control cartilage was significantly greater than any of the treatment groups over any time period ($p<0.05$). The three treatment groups could not be separated statistically and no treatment produced regenerated tissue similar in recovery response to normal cartilage.

Discussion

The advantages of joint motion in promoting neochondrogenesis are well documented.[10,11] The purpose of this study was to compare the biomechanical properties of normal cartilage and those of regenerated cartilage after periosteal grafting and post-operative treatment with CPM, IMM or IAM.

Since this experiment paralleled the histological groups of O'Driscoll[12], his results can be used to aid in the interpretation of the biomechanical results. The grafts in the CPM group were the most dramatic consisting of smooth semi-translucent tissue which was firm and resilient, bonded to the adjacent articular cartilage, and had restored the pre-existing contour of the patellar groove in all cases.[12] The water content of the three groups of regenerated tissue was not significantly different, however, these values were all significantly higher than the water content of normal cartilage.[12] The total amount of hexosamine (glycosaminoglycans) was significantly greater in the CPM regenerated tissue than in either the IMM or IAM groups. The hexosamine content of the CPM group was essentially equal to that for normal cartilage.[12] In the transplanted periosteum there was actually 50 times less hexosamine than that which was in the CPM regenerated tissue[12] thus indicating the ability of CPM to provide the production of glycoaminoglycans in the tissue. Likewise the chondroitin sulfate (the major hexosamine in articular cartilage) content in the CPM tissue was much higher than that of the other two, and was equal to that of the normal cartilage.[12] The Type II collagen content for the CPM regenerated tissue was also significantly greater than that generated by the other 2 procedures; however, in this case the CPM tissue collagen content was also less than that of normal cartilage.[12]

The collagen network together with the hyperhydrated proteoglycans provides resistance to the stresses and strains of articulation. Degenerative changes are associated with softening of the cartilage and a loss of glycosaminoglycans. Being hydrophilic, highly charged and immobilized in the fine collagen network, the proteoglycans impede fluid flow (the lower the proteoglycan concentration the greater the permeability to fluid flow through the cartilage[15]) and resist the compressive loads of joint articulation.[16]

When cartilage is loaded, the load is supported by the collagen proteoglycan matrix and by the resistance generated by fluid movement through it. This matrix comprises an interdependent system crucial to the load-bearing functions of articular cartilage.[17] Hence, failure of the cartilage can be associated with the intrinsic molecular and microscopic structure of the collagen/proteoglycan matrix. With the proteoglycans removed, the water binding potential of the matrix is lost, such that the collagen network responds to the compression as an unsupported fibrous structure, hence the loss of compressive stiffness. Thus a loss of stiffness of articular cartilage can be attributed to an imbalance of the normal constituents of the cartilage.[18]

The stress-strain curve is a good measure of the stiffness of cartilage. Figure 4 reveals that the normal cartilage is far stiffer than the regenerated cartilage stimulated by CPM, IMM or IAM. This should have been expected since after just four weeks the regenerated cartilage is still very soft. Evidence of this can be attributed to the higher water content in the regenerated cartilage as compared to the normal. Also, during the operation some of the subchondral bone was removed and a four week period may not have been adequate to heal the bone plate. If the underlying bone was not as strong or as hard as normal bone there would have been less support for the cartilage when the indentor was applied, making the cartilage appear softer than it was.

As discussed earlier, the CPM regenerated cartilage had a proteoglycan content that was far greater than that of the IAM or the IMM groups. In general, the higher the proteoglycan concentration the lower the permeability allowing fluid flux from the cartilage and hence the stiffer the cartilage. In Figure 4, however, the CPM regenerated cartilage did not appear stiffer; probably because of the effects of the high water content and the soft subchondral bone.

There are two ways of measuring the viscoelastic properties of a material with a load applied to it. The first is by a creep experiment, and the second is a stress relaxation experiment. In this study the stress relaxation experiment was conducted. The stress relaxation of the cartilage is a good measure of its ability to redistribute a load that is applied to it — in essence it indicates the cartilage's shock absorbing potential: the faster the relaxation occurs, the better. Figure 5 shows the stress relaxation for all four groups. As can be seen the best stress relaxation is that of control cartilage. The three treatment groups all have comparably less relaxing ability than that of the control group, but all three are very similar in their abilities to relax. A major factor for this is the softer subchondral bone which in its present state is a deterrent to the cartilages relaxing ability, Close analysis of the shapes of the curve does reveal, however, that the CPM and the IMM curves are more similar in shape to the control than the IAM group

The load recovery is a good measure of the cartilage's ability to recover to its original orientation after having a shock applied to the system. Figure 6 shows the load

recovery for the four groups. As in the other two tests, normal (control) cartilage is far superior to the other groups in its ability to recover. This may be attributed to the softness of the regenerated tissue. This softer tissue is less capable of quickly rebounding from the shock than the stiffer, more elastic cartilage that is present in the untreated joints.

Matrix formation and the interaction of chondroitin and keratin sulphates (the proteoglycan) determine the biomechanical properties of cartilage. Since it has been shown that the proteoglycan content of CPM cartilage is both greater than that of the IAM or IMM modalities, yet equal to that of normal cartilage, a greater length of post-treatment time before testing is needed to demonstrate that the CPM stimulated regenerated cartilage will be biomechanically more similar to the normal cartilage than either of the other two post-operative treatments.

Conclusions

The experimental results have shown that in all three tests the normal cartilage is superior to the three treatment modalities in its ability to absorb loads and then either to relax or to recover from them. The major reasons being the higher water content of the regenerated cartilage and its softer subchondral bone. These were the findings after just four weeks. It would be very interesting to do similar biomechanical studies with a longer post-operative time period — i.e. — one year. Trends relating to shapes of the curves and the keratin sulphate content of the regenerated cartilage would be more definite by then and a more complete analysis could be conducted for the long term effects of CPM versus IAM and IMM on the chondrogenic potential of the periosteum, and the biomechanics of the regenerated tissue.

Acknowledgements

The authors wish to express their thanks to: Dr. Michael Lee, Biomaterials, Faculty of Dentistry, University of Toronto, for his efforts in this project and for his help in the preparation of this manuscript; Mr. Ajai Kumar, senior research surgical technician, Hospital for Sick Children, for performing the surgery on the rabbits and for his advice on how to best take care of the rabbits; Mr. David Abdulla for his expertise in design and manufacture of the mechanical-testing apparatus; and the Medical Research Council of Canada for its financial support.

References

1) O'Driscoll, Shawn. *The chondogenic potential of free autogenous periostial grafts for biological resurfacing of major full-thickness defects in joint surfaces under the influence of Continuous Passive Motion: an expermental investigation in the rabbit.* University of Toronto, Toronto, Ontario. ©1984.
2) Engkvist, Ove; Skoog, Valdemar; Pastacaldi, Paolo; Yormuk, Endem; and Juhlin, Roger. *The cartilagenous potential of the perichondrium in rabbit ear and rib: a comparative study in vivo and in vitro.* Scandinavian J. Plast. and Reconstr. Surg., 13: 275-280, 1979.
3) Ohlsén, Lennart. *Cartilage regeneration from perichondrium experimental and clinical applications.* Plast. and Reconstr. Surg., 62: 507-513, 1978.
4) Engkvist, Ove; and Johansson, S.H. *Perichondrial arthoplasty: a clinical study in twenty-six patients.* Scandinavian J. Plast. and Reconstr. Surg., 14: 71-87, 1980.
5) Pastacaldi, Paolo; and Engkvist, Ove. *Perichondrial wrist arthroplasty in rheumatoid patients.* Hand. 11: 184-190, 1979.
6) Engvist, Ove. *Reconstruction of patellar articular cartilage with free autologous perichondrial grafts an experimental study in dogs.* Scandinavian J. Plast. and Reconstr., 13: 361-369, 1979.
7) Ohlsén, Lennart. *Cartilage regeneration from perichondrium experimental and clinical application.* Plast. and Reconstr. Surg., 62: 507-513, 1978.
8) Ritsila, V.; and Allropuro, S. *Regeneration of articular cartilage defects with free perichondrial grafts.* IRCS Med. Sci. (Connective Tissue, Skin and Bone, Surg. and Transplant) 3: 49-50, 1975.
9) Rubak, J.M.; Poussa, Mikko; and Ritsila, Veijo. *Effects of joint motion on the repair of articular cartilage with free periostal grafts.* ACTA Orthop. Scandinavia, 53: 187-191, 1982.
10) Salter, R.B.; Minster, R.R.; Clements, N.; Bogoch, E.; and Bell, R.S. *Continuous Passive Motion and the repair of full-thickness articular cartilage defects — A one year follow-up.* Orthop. Trans., 6: 266-267, 1982.
11) Salter, R.B.; Simmonds, D.F.; Malcolm, B.W.; Rumble, E.J.; MacMichael, Douglas; and Clements, N.D. *The biological effect of Continuous Passive Motion on the healing of full thickness defect in articular cartilage: an experimental investigation in the rabbit.* J. Bone and Joint Surg. 62A: 1232-1251, Dec 1980.
12) O'Driscoll, Shawn. *The chondrogenic potential of free autogenous periostial grafts for biological resurfacing of major full-thickness defects in joint surfaces under the influence of Continuous Passive Motion: an experimental investigation in the rabbit.* University of Toronto, Toronto, Ontario, ©1984.
13) Kumar, A.; Wond, D.A.; Johnson, R.G.; Herbert, M.A.; and Salter, R.B. The *Restraint of rabbits in a special sling.* Lab. Anim. Sci. 29: 512-515, 1979.
14) Salter, R.B.; Simmonds, D.F.; Malcolm, B.W.; Rumble, E.J.; MacMichael, D.; and Clements, N.D. *The biological effect of CPM on the healing of full thickness defects in articular cartilage: an experimental investigation in the rabbit.* J. Bone and Joint Surg. 62A: 1232-1251, 1980.
15) Mansour, J.M.; and Mow, V.C. *The permeability of articular cartilage under compressive strains at high pressures.* J. Bone and Joint Surg. 58A: 509-516, 1976.
16) Lai, W.M.; and Mow, V.C. *Drag induced compression of articular cartilage during a permeation experiment.* Biorheology 7: 112, 1980.
17) Weightman, B; and Kempson, G.E. *Load carriage, adult articular cartilage edited by Mar Freeman.* London, Pitman Medical pp. 291-331, 1979.
18) Broom, N.D.; and Poole, C.A. *Articular cartilage collagen and proteoglycans: their functional interdependency.* Arthritis and Rheumatism Vol. 26, 9: 1111, 1983.
19) Lee, Michael J.; Nessim, Sherif P.; Kumar, Ajai; and Salter, Robert B. *Biomechanical evaluation of periosteal resurfacing of major full thickness defects in the joints of rabbits: a comparison of the effects at four weeks of Immobilization, Intermittent Active Motion, and Continuous Passive Motion.* Being reviewed for publication in the Journal of Orthopaedic Research.

For All Medical Students
Address U of T
Date December 86

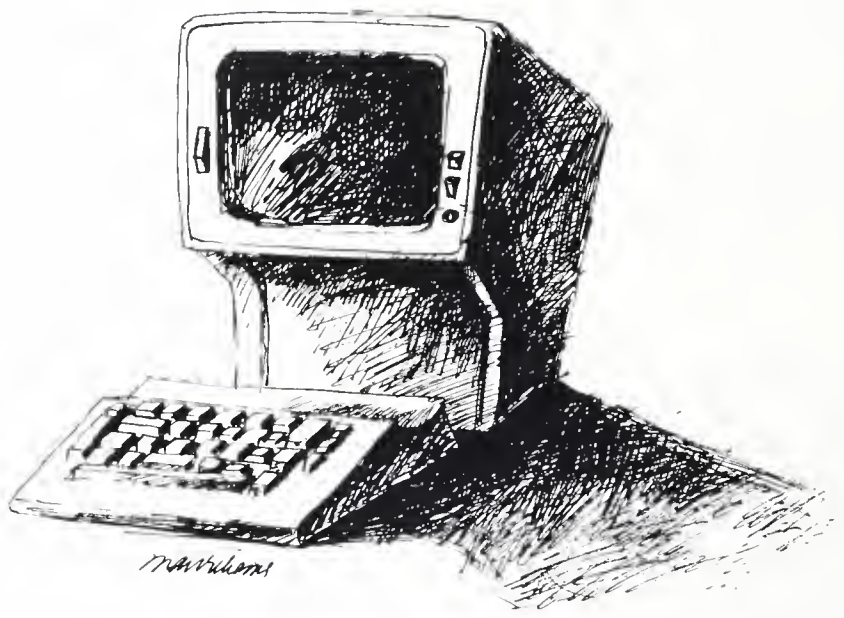
℞ The finest in diagnostic and medical products, all on display in our showroom. — Just waiting for you.

Some Of Our Quality Brands:
Welch Allyn
Taylor (Tycos)
3M (Littmann)
Baum
Ritter
Miltex Instruments
Burdick

Take the subway — Osgoode Stop
10% discount with student card

Hours 9:00 — 5:00
WHITE CROSS SURGICAL INSTRUMENTS LTD
241 Richmond St W, Toronto. M5V 2W3 (Tel. 598-4571)
5155 Timberlea Blvd., Mississauga (Tel. 625-2112)

COMPUTERS AND MEDICINE



It's hard to believe that just a short decade ago, computers at the work place was a rarity and a floppy disk required orthopaedic surgery.

Over the years, many very interesting concepts have been applied to computer programming and, on some occasions, some not so interesting software was the result. Computers have begun to infiltrate the field of medicine like metastases to a lung.

I'm afraid that a recurring dream (a nightmare to some) has echoed in the minds of the experts, a theme that has been stated many times before, will have to be repeated here. Computers are here to stay. They have changed and will change in an even more extensive manner the way of life and practice of medicine.

Beginning with this issue of the University of Toronto Medical Journal, we will be looking at what computers now can and cannot do in medicine — clinical or research. We'll be looking at the ideas behind the technology and the programs that will make what medicine is today and what it will be like for our children and generations to come. It is our hope that this section will portray the state of the art and science of computers in medicine.

Peter Wan, 8T8

HUMAN-80

AUTHOR: JAMES E. RANDALL AND
THOMAS G. COLEMAN, PHYSIOLOGY
SECTION, MEDICAL SCIENCES
PROGRAM, INDIANA UNIVERSITY
SCHOOL OF MEDICINE,
BLOOMINGTON, INDIANA 47405.
COST: $45
HARDWARE: APPLE II/II+/IIE
Z-80 CARD
16K RAM CARD
2 DISK DRIVES
SUBJECT: PHYSIOLOGIC SIMULATION OF THE
HUMAN BODY

HUMAN-80 simulates the physiologic processes in both health and disease. The program operates in three basic modes. First is the experiment mode. Here, one begins with normal physiology and then introduces an insult or disturbance. For example, a hemorrhage can be created artificially and the resulting physiologic response can be then monitored. The second mode is more clinical (and less barbaric) than the first. For this mode, the user has the privilege of playing doctor. There are thirteen patient data files which can be individually called up. Each file contains not only the clinical history but also some selected information regarding biochemistry, urinalysis, etc. In light of this information, a diagnosis should magically appear in the user's mind and based on this diagnosis, the user then attempts to treat the patient — drugs can be administered, transfusions, etc. can all be implemented. Over 70 therapeutic procedures may be performed. The user then monitors the patient by reviewing the effect of these procedures has on various physiologic responses from a menu (figure 1 and 2.) and makes the necessary therapeutic adjustments. One option allows the patient's chart to be reviewed. The final mode is the patient creation mode. New patients can be created and saved on disk for other unsuspecting medical students. So now the user can try and stump friends with bizarre cases.

The strong point of this program is that actual mathematical model of the patient performs quite realistically. There are short-comings. The system is not very user friendly and hence some fumbling through the rather sparse manual is required. It doesn't seem to have been written for the general public. The program runs fairly slowly (479 variables used for the program) and so patience is required rather than an optional virtue. However, the biggest draw-back is the lack of an evaluation of how well or poorly one handled the patient. Some sort of scoring mechanism should have been implemented. The program was designed for a scientist/doctor with some knowledge of physiology. Users with little or no experience will have difficulty using the program. Hopefully, newer versions of HUMAN-80 will show these improvements. But for now, HUMAN-80 is still a pleasant break from reading HARRISON'S PRINCIPLES OF INTERNAL MEDICINE.

Peter Lin, 8T8

MENU OF CHARTS

The Following Charts Are Available:
B: Blood Chemistry
C: Circulation Summary
D: Drugs In Use
G: Blood Gases
K: Kidney Summary
L: Lungs and Vent. Summary
M: Muscle and 02 Debt Summary
P: Pharmacy — Available Drugs
S: Urine Specimen
U: 24-Hour Urine Collection
V: Volumes Summary
Y: Your Patient's Chart
XP: Print Chart X
E: Exit to return to 'COMPUTE'

Figure 1. Screen menu for selection of which of the patient's body functions to look at.

YOUR PATIENT'S CHART

Age: 40 year old male — (Patient # 0)
Height: 175 cm 69 inches
Weight: 80.3 kg 176.7 pounds
Blood Pressure: 1123/ 84 mmHg
Heart Rate: 72 /Min
Temperature: 37.0 Cent. 98.6 F.
Respiration Rate: 12 /Min
Mr. Norm L. Subject
This middle-aged man appears to be in good health, and has no history of severe illness or hospitalization.

Figure 2. Example of a screen display of a normal patient chart.

THE PHYSICIAN'S DATA BASE MANAGER

AUTHOR: N-SQUARED COMPUTING –
ANALYTICAL SOFTWARE
5318 FOREST RIDGE ROAD
SILVERTON, OREGON
97381
(503) 873-5906
COST: $900
HARDWARE: IBM PC/XT/AT/COMPATIBLE
256K
10MB HARD DISK OR TWO 360K
FLOPPY DRIVES
PRINTER, MODEM OPTIONAL
SUBJECT: DIAGNOSTIC AID
DATA BASE OF DISEASES AND
SYMPTOMS, SIGNS, TEST RESULTS
TELECOMMUNICATIONS

Despite the name "The Physician's Data Base Manager" (PDB), this software is not a true data base manage-

PDB/D: MAIN MENU

ATTRIBUTES

A) Enter B) Edit

ANALYSES

C) General D) Essential
E) Weighted F) Bayesian

RECONFIGURATION

G) Drives H) Printer I) Colors

EXIT

J) Telecommunications
K) Data Base Mgmt. L) System

RESEARCH

M) Reference N) Comments
O) Unsupporting attributes
P) Other supporting attributes
Q) Supporting attributes
R) Differential Diagnosis
S) Predisposing conditions
T) Similarly presenting disease
U) Complications
V) DRG Code plus LOS and Reimbursement
W) ICD-9-CM Code

(Please press letter of desired selection)

PDB/D: ATTRIBUTE EDITOR

1	Ascites	7	Dyspnea	13	Retract. lower ribs on inspir.
2	Distension-abdominal	8	Hemoptysis	14	Sputum-blood-streaked
3	Hepatojugular reflex	9	Hemosiderin in sputum	15	Tachypnea
4	Hepatomegaly	10	Orthopnea	16	Wheezing
5	Splenomegaly	11	Paroxysmal nocturnal dyspnea	17	Edema
6	Cough	12	Rales-fine	18	Pallor

<Esc> = Back up <↵> = Main menu <spacebar> = Scroll D)elete

PDB/D: GENERAL RANKING

	Possible diagnosis	Supp. %		Possible diagnosis	Supp. %		Possible diagnosis	Supp. %
1	Cardiac failure	72	10	Common variable immunodefic.	39	19	Bronchiolitis	33
2	Mitral stenosis	61	11	Erythroblastosis fetalis	39	20	Ascariasis	33
3	Cystic fibrosis	56	12	Melioidosis	39	21	Hookworm disease	33
4	Emphysema	50	13	Idopathic pulmonary fibrosis	39	22	Filariasis	33
5	Malignant tumors-sm. intestine	44	14	Plague	39	23	Acute myocardial infarction	33
6	Psittacosis	44	15	Carcinoid syndrome	39	24	Primary cardiac tumors	33
7	Chronic bronchitis	44	16	Chronic constr. pericarditis	39	25	Primary pulmonary hypertension	33
8	Pulmonary embolism	44	17	Strongyloidiasis	33	26	Malaria	28
9	Chron. pulmonary heart disease	44	18	Hodgkin's disease	33	27	Murine (endemic) typhus	28
						28	Infectious mononucleosis	28

Scroll Gener Essen Weight Bayes Refer Comm Unsup Other Supp
Back up Menu Next Differ Predis Simil Comp DRG ICD9CM Report
Use cursor arrows (←↑→↓) to highlight selection, then press < ↵ >.

PDB/D: WEIGHTED RANKING

	Possible diagnosis	Wght.		Possible diagnosis	Wght.
1	Cardiac failure	650	8	Chronic constr. pericarditis	310
2	Emphysema	460	9	Mitral stenosis	310
3	Chronic bronchitis	410	10	Primary pulmonary hypertension	300
4	Chron. pulmonary heart disease	400	11	Acute myocardial infarction	300
5	Common variable immunodefic.	350	12	Bronchiolitis	300
6	Asthma	340	13	Strongyloidiasis	300
7	Pneumococcal pneumonia	320			

Scroll Gener Essen Weight Bayes Refer Comm Unsup Other Supp
Back up Menu Next Differ Predis Simil Comp DRG ICD9CM Report
Use cursor arrows (←↑→↓) to highlight selection, then press < ↵ >.

FIGURES

PDB's main menu is shown. Numerous options are available from this menu and the analysis portion of PDB is based on this.

One sample scenario was typed in and the attributes are shown on the menu labeled "attribute editor". It consists of some of the common symptoms associated with biventricular congestive heart failure or advanced cardiomyopathy.

The general analysis is shown in the figure labeled "general ranking". The top 28 diseases are listed of the over 900 possible diagnoses. The level of support for each disease is also shown.

The weighted analysis is shown in the figure marked "weighted ranking". The list was truncated after a level of weighted suport of 300 specified by the user. In both analysis, cardiac failure was the most likely diagnosis.

ment system. The major portion of the software is an analysis program that allows entry of various clinical symptoms, signs, and test results (all named attributes) and produces a "differential diagnosis". The program comes complete with an extensive preset data bank of approximately 900 diseases ranging from abdominal aneurysm to Zollinger-Ellison syndrome from which it draws conclusions. A total of 1200 possible attributes may be specified. The data bank is based on clinical and epidemiological information from various reputable publications including *The Merck Manual of Diagnosis and Treatment*, *French's Index of Differential Diagnosis*, and *Harrison's Principles of Internal Medicine*. More diseases and attributes may be added by the user if needed.

The result of the analysis is a list of up to over 500 possible diagnoses presenting with the given attributes (or combinations thereof) in order of likelihood. PDB performs 4 different types of analyses on the attributes. A general analysis takes the attributes at face value. An essential analysis puts more weight on the attributes that are required to be present for a specific diagnosis. A weighted analysis takes into account the epidemiological sensitivities of the attributes. And finally, the Bayesian analysis involving multiple steps takes into account the prevalence of the various diseases.

An excellent differential diagnosis is given along with the level of support for each diagnosis provoking consideration of diseases not thought of before. Of course, the software cannot take everything into account (such as onset, duration, severity, etc. of symptoms) but rather only its presence or absence and hence is in no position to replace the human doctor. It does, however, provide a good tool for educational purposes and diagnostic aid.

There are two other parts to the software. A simple data base maintenance part allows editing and displaying of the contents of the data bank of diseases. A simple telecommunications portion facilitates connection to various on-line medical data bases via modem and transfer of information for easy entry into PDB's data bank. All these parts are integrated with the analysis portion.

The software is menu driven and very easy to use with on-line help if required. Simple reports may be generated with ease. The clear and concise documentation is structured around the on-disk tutorial which, like all documentation structured in such a way, is helpful to a certain point but would have been slightly better if it also had separate sections outlining discreet steps on "How to do . . ." various things. It follows an increasingly annoying trend in software documentation that is useful for a "first read" but must be translated into analogous steps if something slightly different has to be done.

The PDB data bank is extensive. However, the prevalence of all diseases was set at 0.0005 defeating the purpose of the Bayesian analysis. I hope that in future this information is updated.

Overall, PDB is a well written piece of software even on the merits of the extensiveness of the data bank alone. It was written in conjunction with a physician. As more information is added, it will become even more useful for doctors and medical researchers.

Peter Wan, 8T8

SYNTEX

Syntex: One of the few companies conducting basic research in Canada.

BOOK REVIEW

The Plague Years

by David Black
Simon and Schuster, NY, 1985. 224 pages.

No disease has touched such deep rooted emotions as AIDs. Homophobia has become rampant and thousands of children, without realizing its implications, carry placards proclaiming "No AIDs in our grades." It would be easy to dismiss *The Plague Years* as yet another contributor to the flood of information, and all too often misinformation, on what some have called the "gay cancer". However, David Black has written a book that goes beyond scientific fact and confronts the fear and prejudice that surrounds AIDs.

As any article or book dealing with AIDs, signs and symptoms of the opportunistic diseases afflicting AIDs and ARC patients are given in a clear, easy to understand manner. He also gives some examples of the public reaction during the peak of the "AIDs scare". Black writes of a customs officer who refused to touch the passport of an American returning from a vacation in Haiti. Even derelicts cross the street to avoid patrons of an AIDs benefit.

The Plague Years also deals with some theories as to the cause and origin of AIDs. The single virus theory ("the virus hits you like a bolt from the blue. What you did has nothing to do with it") and the multifactorial theory ("the disease is a direct result of how you were living your life: going to the baths, being sexually promiscuous . . .") are examined with their moral implications. Black also examines a theory that African swine flu virus is the cause of AIDs. These theories result in competition between various research institutions, universities and indeed, countries. From this glimpse of the scientific community, the media concludes that these scientists were fighting for prizes, research grants and glory — not for the good of mankind. Additionally, Black criticizes the scientific method as "alien to the world of the sexual underground — gay or straight".

Moral issues brought up by politicians, who do not understand the medical facts, and by physicians, who should understand them but often do not, are explored. Some states wish to close bathhouses that allow unsafe sex and enter hotel rooms with undercover public health officers. Two states — California and Connecticut — have made isolation laws all-encompassing so that people may be quarantined on suspicion alone. As one physician stated, the danger of denying the rights of a minority will always exist "as long as there are bigots and being gay is an issue".

As concern over freedom of the press is increasing, Black provides several examples of how that freedom is abused. His award for "worst ever coverage" goes to Geraldo Rivera of "20/20" who said "the nation's blood supply is contaminated and the 'safest thing to do is store up your own blood' ". But the lay press is not solely responsible. The February 1984 edition of *The Southern Medical Journal* contained an editorial suggesting that AIDs is "a fulfillment of St. Paul's Pronouncement: 'the due penalty' for the error of men who 'abandoned the natural function of the woman and burned in their desire toward one another. . . .' "

Black's writing style is effective and the development of material and his own reactions is excellent. Throughout the book, he often enters a philosophical stream that becomes a frantic pursuit to understand a spectre that fascinates, and at the same time, horrifies him. In the process, David Black comes to terms with his own feelings through a journey that hopefully his readers will join.

Janis M. Miyasaki, 8T8

Healing the Wounds

by David Hilfiker, M.D.
Pantheon Books, New York, 1985. 209 pages.

For those who have ever been troubled by an ethical dilemma, have ever been involved when a patient died, or, have ever lain awake at night feeling the daily anxieties of medicine wash over you, Dr. David Hilfiker has written for us, through his professional autobiography, an analysis of the problems and stresses that assault physicians, and some possibilities for how we can cope with them.

"Healing the Wounds" is the reflections of a "real" physician on what he has discovered about himself, and his own special situation, and how his concerns are a product of the stresses and difficulties that all physicians face.

Dr. Hilfiker worked as a general practitioner in the clinic/hospital of a small town in northern Minnesota. Eventually, the stresses and anxieties of his position forced him to leave medicine for a while, to evaluate his life and his feelings about being a doctor. The book is written during this period, and is an attempt to share with us the experience of his growing awareness of the stresses that assaulted him, his analysis of them, and the changes he subsequently made in his career that allowed him to come back to the practice of medicine.

These "stresses" of medical practice are divided by Hilfiker into two groups. The first consists of the daily stresses that are inherent in the nature of a doctor's work — the intensity of the work, the need to be available, the vast knowledge requirements, the uncertainty, the fear of mistakes and the constant ethical dilemmas. We are all somewhat aware of these after our second year lectures in Community Health. However, the second group are more interesting. Hilfiker sees these as arising from the responses that doctors come up with to deal with the first group of stresses. That is, while distancing oneself from a patient may be a way to cope with some of the anxieties of dealing with that patient, if this becomes a fixed way of behaving, it can develop into a problem in its own right. Furthermore, he points out that money and prestige develop into new values in practice, as they become compensation for the stresses suffered by doctors. But these then become stresses themselves — they begin to take control over one's practice, and represent unsatisfying and unattainable goals.

This second group of stresses appears to be much more important to Hilfiker; the first group is built into the profession, but the second group can be mitigated by restructuring the practice of medicine, and approaching it

with new attitudes. Hilfiker goes on to explore this in the last chapter, entitled, "The Wounded Healer".

I was pleased to see that Hilfiker did not just present the problems, but also dealt with some possibilities for coping with these problems. I think that he makes some very valid suggestions about ways in which we can deal with or remove the stresses that arise. He is certainly very realistic about the potential for change in the profession. But he does tend to deal mainly with his own set of problems rather than those that are of more global concern to physicians. For example, it becomes readily apparent that he has a lot of trouble with the question of money. I agree with many of the points he makes about the inequality of salaries among health professionals, and the antagonism that physicians' large salaries create between doctor and patient. His suggestions for dealing with this, however, are not for the faint of heart.

Hilfiker also tends to adopt a verging-on-holier-than-thou tone in this last chapter. His discussion of the doctor as "The Wounded Healer" I found a little confusing, and rather too spiritual to be taken quite seriously. On the other hand, coming away from it with the sense that, "Isn't it a wonderful thing to be a healer, a servant of mankind, and though there are stresses and tensions, I can learn to deal with them, and use these "wounds" to my advantage in healing others . . ." is not altogether a bad thing, after having been faced with his quotations of the suicide rate among doctors.

Dr. Hilfiker has directed this book to three audiences. The first, of course, is doctors. I think he justifiably points out the importance of his book to this group, because neither the structure of the profession, nor society in general, equips doctors and students to deal with the pressures he has been discussing. Certainly, the book allows us to recognize these stresses, their effect on us, and encourages us to find ways of dealing with them.

The second "audience" for this book is other health professionals. These other health care workers, particularly nurses, are intimately bound up in the hierarchical structure in which doctors operate. As Hilfiker points out, not only can they be the unfortunate recipients of the products of the physician's stresses, but their relationships with doctors (and here I am referring to professional relationships) can be the source of further stress for doctors. Thus, in reading this, Hilfiker hopes that they will learn to empathize with doctors, and that there will be a mutual recognition of the need to work together as a team, and thus remove one source of stress for both parties.

Finally, this book has been written for the lay public. "Doctor Stories" are a hot item, and I am sure Hilfiker is counting on this to attract readers. However, they will be surprised to find that this is a story about "Joe-Doctor", and that neither he, nor the rest of us will ever be the completely selfless, devoted models of perfection represented by their television ideals. What they *will* get is some insight into their doctors' lives, which will hopefully generate some empathy, rather than antagonism towards doctors. Perhaps this will ease some of the frustration and anger felt by those who have ever had less than satisfactory treatment in the emergency room, or a long wait in the doctor's office. Personally, I can think of many critics of medicine who would benefit from reading this book.

Despite the occasionally maudlin writing, and the sense of anxiety that seems to pervade the book, I was quite satisfied with "Healing the Wounds". I think it provided a good discussion of the stresses of doctoring, and how we can shape our attitudes to help us cope. By making us aware of the stresses we face, Hilfiker has, essentially, armed us for battle. I do recommend the book, particularly for medical students. I don't think its message should be accepted religiously, but should be considered, and perhaps stored away for reference at a future date. Then I think the book would best be given to one's mother, or a friend, to be taken with them next time they are sitting, waiting in a doctor's office.

Lori Albert, 8T8

Encyclopedia of Medical History

by Roderick E. McGrew

New York. McGraw-Hill Book Company, 1985. Pp. xiv + 400. $50.95

The *Encyclopedia of Medical History* is a concise text aimed at stimulating interest in a subject too often ignored by physicians. Initial perusal of the table of contents, however, produced misgivings which were subsequently borne out by a more thorough appraisal. There is something incongruous about the presence of a table of contents in a book purporting to be an encyclopedia. Indeed, whatever else it may be, the book reviewed is definitely *not* encyclopedic.

In the preface, the author states that the purpose of his work is "to provide an easily accessible historical treatment of important medical topics. . . Each entry has been conceived as an independent essay covering the stated topic chronologically" (p. xiii). Herein lies the problem; for this is more accurately a collection of essays — 103 to be precise — each with a short list of references and a minimum of cross-referencing. In themselves, the compositions are concise, clearly written and often interesting.

> *"Did you know that, prior to the invention of obstetrical forceps, if a mother was unable to deliver her child owing to a small pelvic opening, hooks called 'crochets' were used to dismember and remove the child? Alternately, a craniotomy could be performed on the infant, the hole in its head providing a purchase by which the baby was then dragged out. Of course, mother and child often died. Forceps were invented in the early 18th century by the Chamberlens, an English family of male midwives, who kept their invention a closely-guarded family secret for almost a hundred years in order to out-perform their competition and thereby increase their personal wealth."*

A major detraction is the lack of a comprehensive approach to the history of medicine. Instead, the choice of "important medical topics" appears arbitrary. In an effort to appeal to the broadest readership, including historians, health care professionals, and the lay public, the subjects presented range from synopses of entire branches of medicine (e.g. Neurology, Ophthalmology) to medical curiosities (e.g. Mesmerism, Quackery). Yet

the *Encyclopedia of Medical History* contains omissions, oversights and inconsistencies. It is not clear why there should be an entry on 'Medicine in Mesopotamia' while a chapter on Islamic medicine is conspicuously absent; why quinine should warrant separate discussion, but not, for example, opium or digoxin; or why African trypanosomiasis is afforded a six page treatise when the whole subject of medical genetics is ignored outright.

Another shortcoming is the lack of biographical essays. The reader interested in learning about Pasteur's contributions to medicine should not have to leaf through a dozen index entries in a book claiming to be an encyclopedia. Equally surprising is that barely a couple of lines are devoted to so eminent a personality as Sir William Osler. At least he is included; Werner Forssman, a Nobel laureate for his self-experiments in cardiac catheterization, apparently did not impress Professor McGrew sufficiently to merit even passing mention.

The *Encyclopedia of Medical History*, by attempting to offer too much diversity for too varied a readership in too brief a volume, was destined to fall short from the outset. Thus, in its present format, it cannot claim to improve upon existing works of reference. On the contrary, because information is not always readily obtainable simply by looking for the topic of interest as a separate listing, a convenience expected in such a book, it is inferior to most other medical encyclopedias already on the market. This is unfortunate since, in general, the essays are informative and make easy, enjoyable reading. If only the book had been marketed as a collection of essays rather than as an encyclopedia, there would have been less to criticize and more to recommend.

> *"Have you ever heard of the medico-historical enigma known as the 'English sweating sickness' which appeared and then disappeared in the 16th century? Healthy, well-fed adults would collapse and die within 24 hours of acquiring a violent, soaking, stinking perspiration, accompanied by pains in the head and stomach, and an excruciating sensation of internal heat."*

Jafna Cox, BA, 8T8.

The Man Who Mistook His Wife For A Hat and other clinical tales

by Oliver Sacks Summit Books, New York, 1985; 233 pages

Oliver Sacks' book is more than neurology for the layman. It is a graceful exploration of the human sides of those afflicted with neurological defects. Sacks is a scientific humanist — his personal search for the poetry of life has led him to neuroscience. Within the introduction itself, he calls for a little more romance to clothe his science. Thus he joins the grand tradition of modern scientists who try to reconcile their external science with their inner esthetics. Sacks' book embodies a commodity in short supply: a thoughtful blend of art and science used for the mutual complementation of the human mind.

The book is divided into four parts, ominously titled — 'Losses', 'Excesses', 'Transports', and 'The World of the Simple'. In each section, there are approximately six case descriptions — some bizarre, some poignant. Consider the title story, 'The Man Who Mistook His Wife for a Hat'. This is the case of an accomplished musician, a Dr. P., who continues to be a respected music teacher, but who nevertheless suffers from a profound visual agnosia. Dr. P.'s mind has become computer-like, seeing details but not the whole, missing the Gestalt, and gradually becoming less and less familiar with his visual world. Only music remains a conquered entity. Consider this:

> *"For not only did Dr. P. increasingly fail to see faces, but he saw faces when there were no faces to see: genially, Magoo-like, when in the street, he might pat the heads of water-hydrants and parking-meters, taking these to be the heads of children; he would amiably address carved knobs on the furniture and be astounded when they did not reply. . .He. . .started to look around for his hat. He reached out his hand, and took hold of his wife's head, tried to lift it off, to put it on. He had apparently mistaken his wife for a hat! He wife looked as if she was used to such things." (p. 7)*

Sacks views the same title story concerning Dr. P. as a methaphor for Medicine in general — the overemphasis of details with the gradual distancing of the human world with its sentiments and values. Sacks writes:

> *"Our cognitive sciences are themselves suffering from an agnosia essentially similar to Dr. P.'s. Dr. P. may therefore serve as a warning and parable — of what happens to a science which eschews the judgmental, the particular, the personal, and becomes entirely abstract and computational." (p. 19)*

Throughout the book the case descriptions reach the level of the bizarre: people with non-existent phantom limbs which are nevertheless painful; a man who can form no new memories, for whom time stopped in 1948; a young cocaine-addict medical student who, having dreamed he was a dog, had gained a profound olfactory sense which became the center of his life; and so on. It is inspiring to see that even in the midst of such tragedy, despite so much invasion into a person's sense of self — nevertheless a fundamental human dignity can be maintained.

One wishes there were more books such as this one. The neurology is incidental and the focus is on the human and humane element. Oliver Sacks had previously established quite a clinical-literary reputation with his books *Migraine*, *Awakenings*, and *A Leg To Stand On*. *The Man Who Mistook His Wife for a Hat* has been on the New York Times Best Seller List for several weeks and so the reading public has also recognized the book for what it is — Art.

Shafiq Qaadri, 8T8

The Making of a Psychiatrist

by David Viscott, M.D.
Pocket Books, NY, 1986
$5.95

Novels written by physicians for the general public are often cynical and frequently confessional in nature. A well known example of this is *The House of God* by Samuel

Shem, M.D. This book is certainly M*A*S*H meets the metropolitan teaching hospital minus the lighthearted sense of humour. A gentler cousin of this novel is *The Making of a Psychiatrist* by David Viscott, M.D. It too, deals with the training of a physician but attempts to offer insight into a doctor's life as well as entertain.

Dr. Viscott was a professor at Boston University Medical School and author of *The Language of Feelings*, *The Viscott Method*, *Risking* and *How to Live with Another Person* (a book certain to be of value for readers of this journal). Although the first chapter is somewhat clumsy, Dr. Viscott quickly finds a fluid style as he deals with his residency years in psychiatry.

An appealing aspect of this book is Dr. Viscott's sense of humour. It is self-effacing without being vicious. As well, the inadvertent comedy found in a hospital is presented without oppressive cynicism. The inevitable stories of physician incompetence are present, but Dr. Viscott does not condemn all physicians, as others have done. Instead, he tries to accept that there is a wide range of ability in this profession.

Readers will appreciate this book as a welcome change from lectures and texts, since Dr. Viscott deals with psychiatry as your grandmother would — with common sense and a minimum of jargon. When he was unsure of his direction with a patient, he asked " 'Will what I am doing help the patient?' It hardly ever let (him) down". Not only is this an entertaining psychiatry primer for third year medical students, it offers free advice for patients in psychotherapy in the final chapter.

Included for good meaure are accounts of his "miracle cures" that come just when he and the reader have almost given up hope. Yet, because of (or in spite of), his medical training, Dr. Viscott never stops caring about his patients. Yes, you can be friends with your patients and still be a good doctor.

In reflective moments, pearls of medical wisdom are revealed. Doctors should remember that both they and medicine are fallible. Perhaps, most importantly, Dr. Viscott writes, "I wasn't trying to solve the problems of mankind, I only wanted to fulfill myself and be happy in my work. . .my joy would first have to come from my work itself, from being me, myself."

Dr. Viscott tells his story well — with candor and compassion. This is a novel well worth reading for its rare insight into the medical profession by a physician who still finds joy in his work.

Janis M. Miyasaki, 8T8

Bedside Manners: The Troubled History of Doctors and Patients

by Edward Shorter
New York: Simon & Schuster Inc., 1985. 316 p.

Dr. Shorter makes an eloquent plea for "patient-oriented" rather than "disease-oriented" medicine in his *Bedside Manners* book. He deplores the search for organic causes for disease in every patient interview the beleaguered doctor conducts. His book is well-researched and tries to be fair. Sometimes however, the attempts to explain patient and doctor attitudes in separate chapters under broad and arbitrary headings of traditional, modern and post-modern becomes cluttered and confusing. Dr. Shorter illustrates and characterizes through anecdotes and quotes the patient and doctor of each era spanning the time period from 1750 to present day.

Though well written, this is not a book for browsing — the sheer density of footnotes per page clearly attests to that. Too often, by trying to be historically complete, the main thrust of this book is lost.

What does come to light are some fascinating insights of how an outsider sees medicine. In surveys and personal interviews with patients and doctors, Dr. Shorter is quick to point out the impasse the patient-doctor relationship has become. Neither one party is at fault. The patient advocacy stance and the 'new' scientific approach in medicine have developed and grown. Both serve to exacerbate the tension.

The author also makes a pitch for the psychosocial causes and treatments of disease towards the end of the book. Perhaps his focus on patient and doctor leads him to overlook the disease. No one can wish to go back to the atrocities of medical practice where the touch of the physician-surgeon was often the touch of death. And surely the prospect of single disease-oriented practice is unappealing. Preventive medicine is not mentioned as a viable alternative and becomes a serious shortcoming in retrospect.

Though interesting and fascinating in spots, this book falls short of its goal.

Miah Hahn, 8T8

HEINE

DIAGNOSTIC INSTRUMENTS TO MEET THE HIGHEST STANDARDS

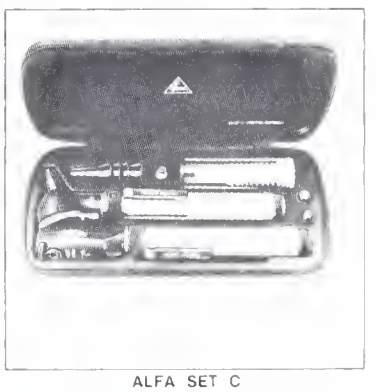
If only the best materials are used, if assembly is carried out with meticulous care and rigid quality control is applied, the result is top quality, high performance equipment

This is exactly how HEINE became the world's leading manufacturer of diagnostic instruments

HEINE offers you an unrivalled selection to meet the most demanding requirements of the medical profession

FIBRALUX SET

3.5 volts Kryptogen (rechargeable)
all glass optics
coaxial optics ophthalmoscope
all metal casings
dual purpose fiber optic otoscope
cobalt blue filter
spare bulbs included
disposable and reusable specula
catalogue number A 14 20 313



ALFA SET C

2.5 volts Kryptogen
rechargeable or AA size batteries
coaxial optics ophthalmoscope
fiber optic otoscope
spare bulbs included
disposable and reusable specula
catalogue number D-292 10 022

FEEL FREE TO CONSULT US AT HEINE INSTRUMENTS (CANADA) LTD OR THE J. STEVENS CO. LTD

HEINE INSTRUMENTS (CANADA) LIMITED

STEVENS

Thoughts on a streetcar going west

I tasted of death tonight;
a bilious, stainless-steel, florescent-light death
with the taste of a rotting pomegranate
— like many, I suspect.
When my friend died, I tasted it too;
tasted relief; tasted the staleness of dried hope,
and sour nights;
tried to find a taste.

I was impressed by the evisceration,
though it made me nervous.
Too easy, it seemed, to take a man apart,
inside-out, just to weigh the organs.
You would have liked it, John — such restraint;
a sacrifice with such purity of intent,
such economy of means for such a task.
The art of laying bare.

We talked of death.
Last week in Jamaica . . . she fell before he swung . . .
split her skull on the toilet . . .
two years less a day . . .
I was thinking would they notice if I threw up.
For there was John as calm in life as after,
his young, aged hands exhorting us to see
what death was telling him.

Oh, yes I liked them,
Those white-booted butchers, splattered and smiling.
They, at least, give death a taste
before perfume and phrases wash it away.
Because somewhere between strength and weakness, John,
we forgot to scream — forgot an arc of howl
across the night with our withered anger
— forgot to stop shaking hands.

Kingsley Watts, 8T7

How I wasted my prime

You've got me looking into the mirror in the
Burlington Plaza cinema men's room
Inspecting my pimples and wondering why I came so far
to walk around the park a couple of times
And listen to stories about your uncle Jim
You smoke too much
And you don't quite fit in with all those stories I thought up for you.

You were supposed to be that face that looks best in mosaic
You were supposed to be that woman readied with an asp in her basket
You were supposed to have been burned at the stake
for some heresy I had authored

But instead of a bleeding relic reverently guarded by silent monks
I found a part-time cashier at Dominion Food Mart
Did I tell you you smoke too much?

Stephen Starr, 8T7

To Grandad – With Love

It was a beautiful, beautiful, sunny day
But really it shouldn't have been that way.
He lay there so still, so calm, and so white
But somehow, yet somehow, he didn't look quite right.

I wanted to remember a tall, stately fellow,
Now a lifeless creature of white and of yellow.
I wanted to hear the stories of old
And not see the lips so quiet and cold.

It was sad, there were tears, and prayers to be said
And there lay my grandad, grandad was dead,
But the trees were still talking, the flowers still growing,
The sun was still shining, and the wind gently blowing.

And beyond this peace, the cars zoomed by
And so many people didn't know to cry!
People were walking with eyes looking ahead.
No one realized my grandad was dead.

The world can't stop when I'm feeling sad
And it won't rejoice when I'm feeling glad.
One man is born, another one dies
But the sun will still set, and the sun will still rise.

Suzanne Shephard, 8T9

Remembrance

Below the sun that climbed above the tree,
I felt the power of words and touch that sent
My heart to heave, but not the Guardians Three:
Religion, Race, and Culture. They never bent.
I straddled the fork that tore our friendship in half,
I prayed for strength to walk the path unknown,
I failed. The ageless Guardians sneered and laughed,
"He never saw the seeds of failure sown."
Remember the days when we felt green and young
And knew that love could conquer death and fear?
Now in the shadow of the blooming sun,
They stripped from me the one I held so dear.

But still I'll say, to show those Jealous Three,
"I love you." Though some things can never be.

Ambrose Cheng, 8T8

Promise of Second Chance

James Kim, 8T9

I've waited seventy-six years for you. Any day now I'll see you. Oh, will you come to me this time like you did then? Will you keep your promise to me? I have grown old; yet, I haven't forgotten. The memories of you are all that I have left. Please, let this, my last, beautiful dream come true.

He is just an old man looking at the night sky as if his life depends on it. He curses the overcast heavens, his mind nursing the secret memory of his only treasure. He feels the chill of the night air and hurriedly heads home.

He lives alone in a sparsely furnished bachelor apartment. The building is perched on the side of the highest hill in the city. The air is thin but clean, and a slight, constant wind blows away the smell of dirty concrete and car fumes. He can see for miles around from his window — quite the vantage point, quite the reflection of his life.

He is ninety-six years old, but he looks little older than sixty. Life has treated him well; he has no complaints. As he bided his time, friends — few and far between, and even then far, far away — have come and gone. His is a private life.

I have lived my life only in anticipation of you. You gave inspiration with your presence. And I have kept you to myself. Are you not a special gift to my heart and soul? I could never share what you gave to me. You have to come back to me.

He walks constantly. His stride belies his age; there is no weariness as youth courses strongly in his blood. But time has still wrinkled and weathered the shell. He has travelled further and longer than any man before him, and the sights he has seen are collections of precious images, evoking hidden emotions. Now he has returned to his starting point — the same place but seventy-six years away — to meet the end. He will be a part of it, or die. Either way, the moment approaches relentlessly.

I see another sunset. I have lost track of which one this is. Oh yes, I have been counting. I started counting when you first left. Can you remember, like I can?

The sky is clear tonight. Just look at that. The stars. . . . No matter what I was witness to, it still takes my breath away. And you are out there.

Waiting is one of the hardest things about life. Waiting means time to think. Waiting means time to imagine. Waiting is jumping into black, swirling water unsure of how deep it is or what writhing, sinewy creatures prowl therein. It is an irreversible step, a head-first plunge that can only be stopped by its sudden end.

Patience, old man, patience. No need to tell him, for he endures a wait stretching more than a time interval; it spans the width of the mind and the depth of the heart. Another night goes by, so he ages one more day into the next sunset.

I don't know how long I can keep this up. I can't breathe too well climbing up this bloody hill. Come on, make it worth my effort; clear up, for chrissake, let me see the sky.

He shivers and feels the hairs on his arm stand on end. A slight wind runs through his white hair. The clouds open up: nebulous lids opening on a glittering, heaven-borne treasure box. His eyes turn to the right.

Baby, there you are! Don't pass me by now. I'm calling you. Can you hear me? Look at me! I know you're too far away, but I'll be here tomorrow. I never doubted; yet I never thought I would feel so good. Yes! tomorrow and tomorrow. . . .

He is close to fulfillment. One more day — the longest day he will ever live — until his dream is manifest. It will be the most difficult period of his life, so near the culmination of his existence. But sleep comes to him readily, with no dreams to spoil the dream he is living.

He awakens as the first light splits the horizon. There is so much to do. He chuckles as he realizes that he has done nothing since moving in. To whom will he leave his worldly possessions, he wonders. He has no one now. And suddenly the loneliness churns his stomach. He gasps in the backdrop of a fantasy for all the things he has never experienced. No one can have it all.

He spends the day cleaning his apartment meticulously. That room will be the only legacy of his life. Finishing, he wipes his forehead with the clean side of a dustry rag. Then he reflects sardonically at the cruel reality of transience: nothing except a few pieces of clothing in that room is his; everything is rented. And when he is gone, they too will disappear, scattered to other places, wrenched away from the magic of their special unity in that room.

The day darkens, and he knows that he goes out the door for the last time. He thrusts his hands in his pockets, and touches the cool metal of his remaining coins. He has spent wisely, knowing just how much to earn and spend and to have nothing left in the end.

As he approaches the steep path to the lookout, he gives thought to what he leaves behind. Nothing, he leaves behind nothing. He grimaces and curses beneath his breath. He cannot imagine anything being erased away so cleanly than his existence today. He angrily wipes at a tear-laden eye and starts to ascend.

The climb is easy for a boy of twelve, but brutal for a man of ninety-six. Each breath is a superheated inflow of furnace air. His nostrils flare to ease the burning. Sweat beads his forehead just below his hairline. His lips tremble, and colour drains from his skin. He gasps in physical pain and collapses prostrate on the dusty path. His mouth wets the dry earth that is drawn in with the first breaths. He coughs and wheezes, but he cannot move.

Thoughts jackhammer through his skull: "Now now, not now! Godammit! just give me a bit more time. Let me

live for five more minutes."

The paralysis and numbing fade away erratically enough for him to roll over and spit out the dirt. His chest still heaves below his head, seething with a maelstrom of emotion. He cannot stop now; but, the body cannot obey the mind. The horror attacks him: he sees himself as a pathetic, dying old man clinging onto the barest promise of a dream.

His thoughts are broken by the rustle of bushes at his feet.

"Hey, mister, is everything all right?" It is the voice of a small boy.

The old man strains to see who addresses him. He cannot distinguish the figure in the shadows but speaks nonetheless:

"Must have had a heart attack, son." His voice is raspy, and the words seem far away. He reaches out his arm for support.

"Give me a hand up, son."

The hand he receives is pitifully small, but he manages to stand upright. His hand falls on the boy's shoulder.

"Hey, shouldn't you go to a hospital?"

The grip on the shoulder tightens desperately. The old man breathes heavily.

"I want you to take me up to the lookout, boy."

"You're hurting my shoulder." The lad struggles. "Let go! What are you anyway — a faggy pervert or something?"

The effort of just standing and speaking exhausts the old man.

"Look, kid, just help me up to the lookout; I'll give you some money for your trouble, okay?"

"How much?"

"Everything I have!" He is not joking.

"And I just have to take you up there?"

"Now! not bloody next year —" He coughs, "— let's go!"

The rest of the climb is in silence except for the sound of shoes on the dusty path and rhythmic, heavy wheezing. The boy cradles the old man's waist as they step over the clumps of rocks imbedded in the soil. They break into the clearing at the top of the hill. The boy guides the man to a large boulder and watches him sit down. He stands expectantly, his hands fidgeting at his sides.

"So where's the money?"

The man digs in his pockets and takes out his coins. He gives them with trembling hands to the boy.

"Sixty-seven cents? You've got to be crazy, mister — I did all that for sixty-seven cents? — "

The old man is not even listening, his face is toward the night sky. He points suddenly overhead.

"Quick, son, what is that?"

The boy looks up, following the outstretched arm.

"It's Halley's Comet, mister."

The old man smiles contentedly and closes his eyes.

"How old are you?"

"Thirteen, but that's none of your business."

There is a moment's silence.

"I saw this beautiful light seventy-six years ago; I was twenty then. It came to me, *to me*. She came to me. You could never know what she meant to me; what she taught me, what she made me feel in that one night.

"She was shrouded in a gossamer that shimmered like a fountain of stars. Her face was beautiful — her eyes blazing; I couldn't look straight at her. And her voice was everywhere, the purest melody to touch my soul. She brushed by me, and her touch was the heat of white fire, but cast the lingering coolness of blue ice. I loved her; I love her. And she's coming back tonight, just like that night — when I lived a lifetime."

"If you could just glimpse into the morning of my life, you'd taste the magic of uncharted emotions."

He is oblivious to everything but his thoughts. He points to his head and then his heart.

"It's all in here. She really hasn't left, you see, just waiting for the right time to come out. For anything, for anyone to be real, you've got to believe. That's what she taught me — and I'm telling you now. There is nothing you can't see. There is nothing to hold you back. You've got everything already here, waiting — all the worlds this universe has to offer."

"I've seen things you couldn't picture in your wildest dreams — blossoming sunbursts framing the windows of my imagination: I've touched the crystal snow under an orange moon; I've smelled the fragrance of iridescent nebulas; I've walked the celestial path of angels into the hearts of suns; I've danced in the fleeting veils of cosmic winds."

"Everything, except her — I could never find her because she knew I was looking. But she's coming to me now. . . ."

His breath shortens again, and the pain stabs anew. He clutches the shirt above his chest. The boy stands in alarm, unsure of what to do. He is a witness to the purest form of madness, the passion of inner convictions. He still reels from the blows. With a sigh, the old man loses consciousness and slides off the boulder.

The boy takes a step towards the prone figure but stops, for he senses that he intrudes on the sanctity of a final gesture. He turns to leave, in the hope that when he returns with help, the old man will have succumbed under a blanket of stars and the arching stardust of his beloved comet.

There is light everywhere. A sound of incessant breeze brushes pleasantly against the stars. One voice, a musical voice, sails on this wind.

"I've come back for you. Come, touch my hand."

"I've waited long. I never stopped loving you." The responding voice is young and strong.

The slightest murmur of a laugh rings delicately in the air to show appreciation.

"No, you haven't. Will you leave with me? We are together, forever."

"I've done so little with what you gave me. . . .Can you still look at me the way you did then?"

"You've done more than you think with my little gift; I never doubted you, now fly with me; our wait is over."

The police man scolds the boy for making mischief; he will take the boy home to face his parents. The stretcher-bearers make their way back down from the lookout to their ambulance, carrying an empty stretcher. As the boy leaves, he fingers the coins in his pocket and he looks at the distant comet. Up there is the secret and the knowledge he shares only with the stars.

Patrons

The Journal staff and Medical Society wishes to thank the following patrons for their generous support.

Dr. Sharon M. Abel
Dr. Uwe Ackermann
Dr. Paul Adam
Mrs. Elizabeth Akesson
Dr. Peter W. Alberti
Dr. B.M.E. Allan
Dr. E.C. Allen
Dr. Douglas Alton
Dr. Dominick Amato
Dr. Ulo Ambus
Dr. William Anderson
Dr. Crawford Anglin
Dr. Harvey Armstrong
Dr. M. Arstikaitis
Dr. Sylvia L. Asa
Dr. J. Gary Ashby
Dr. Mary Jane Ashley
Dr. Harvey L. Atin
Dr. Michael Baker
Dr. B. Balshin
Dr. Eric J. Barker
Dr. Marshall Barkin
Dr. P.A. Barreca
Dr. Colin Bayliss
Dr. Barbara Blake
Dr. Lindsay Belch
Prof. Margaret Baigent
Dr. Jack Barkin
Dr. John A. Beswick
Dr. Jan Blumenstein
Dr. Charles B. Brown
Dr. Alan Bruce-Robertson
Dr. P.J. Brueckner
Dr. Martin Buckspan
Dr. Yvonne de Buda
Dr. Gerald N. Burrow
Dr. David S. Byers
Dr. Doreen Campbell
Dr. L.E. Cappe
Dr. K.C. Carstairs
Dr. Daniel C. Cattran
Dr. A. Cecutti
Dr. Alex Chan
Dr. W. Chan
Dr. Morris Charendoff
Dr. Ricahrd Charron
Dr. Peter Chin
Dr. Robert Chisholm
Dr. Bernhard Cinader
Dr. Edward H. Cole
Prof. A.W. Conn
Dr. George Connell
Dr. John Connolly
Dr. Donald Cowan
Dr. Donald Currie
Dr. Derek A. Davidson
Dr. John K. Davidson
Dr. Heather R. Dawson
Dr. Mervyn Deitel
Dr. Paul Dedumets
Dr. Christine Derzko
Dr. G.O. Devilla
Dr. H. Roslyn Devlin
Dr. Dale Dotten
Dr. James Dubbin
Dr. Hames Duffin
Dr. Stuart Z. Dyment
Dr. John Edmonds
Dr. Robert Ehrlich
Dr. M.K. Gospodarowicz-Evans
Dr. W.H. Fader
Dr. Ronald Fenton
Dr. John Finlay
Dr. Edward Fish
Dr. J. Fleming
Dr. R. Fleming
Dr. W.C.F. Forder
Dr. Peter J. Fouix
Dr. Rodney Fowler
Dr. William Francombe
Dr. Jeremy Freeman
Dr. L.E. Fremont
Dr. Arnis Freiberg
Dr. Norman E. Fremes
Dr. A.E.M. Geisler
Dr. Richard M. Gladstone
Dr. David M. Goldberg
Dr. Melvyn Goldberg
Dr. Michael Goldberg
Dr. Barry J. Goldlist
Dr. Irvin Gollish
Dr. J. Gollish
Dr. Maria Gospodarowicz
Dr. Avrum Gotlieb
Dr. Robin Gray
Dr. David Greyson
Dr. A.E. Gross
Dr. L.F.L. Grover
Dr. J. Gruss
Dr. Michael L. Guinness
Dr. Philip Halloran
Dr. & Mrs. Abraham L. Halpern
Dr. Mitchell Halperin
Dr. Walter J. Hannah, The Hannah Institute
Dr. Gordon D. Hardacre
Dr. John Harkins
Dr. Ian Harrington
Dr. I.G. Hastie
Dr. Gerald Heasman
Dr. Anne Hedlin
Dr. R.D. Henderson
Prof. E.B. Hendrick
Dr. S. Hichman
Dr. R.C. Hicks
Dr. H.Higgins
Dr. F.M. Hill
Dr. Charles Hollenberg
Dr. Stephen Holzapfel
Dr. W.J. Horsey
Dr. Robert Howard
Dr. Michael Howcroft
Dr. Kirby Hsu
Dr. Shao-nan Huang
Dr. Gordon Hunter
Dr. Paul A. Hwang
Dr. R.H. Hyland
Dr. M. Hutcheon
Dr. Stephen S. Im
Dr. Mary V. Jackson
Dr. Robert W. Jackson
Dr. D.G. Jagdeo
Dr. Duro Jakasa
Dr. Christopher Jamieson
Dr. Moray G. Jansen
Dr. D.A. Jarvis
Dr. Michael Jewett
Dr. Donald P. Jones
Dr. Albin T. Jousse
Prof. Nancy Joy
Dr. Ana Marquez-Julio
Dr. Louise Keevil
Dr. H.W. Keller
Dr. J.D. Kempston
Dr. & Mrs. A.J. Kennedy
Dr. Tom Keogh
Dr. I.G. Kerr
Dr. J. Keystone
Dr. Hollister King
Dr. Max Kleinman
Dr. Bruce Knox
Dr. Arnost Kolin
Dr. Irvine A. Korman
Dr. Bernard Langer
Dr. Edward Lansdown
Dr. Carol P.Y. Lee
Dr. Wolf-Deitrich Leers
Dr. S.L. Librach (Family Practice Unit, Toronto Western Hospital)
Dr. Gordon Lickrish
Mr. Sidney Liswood
Dr. H. Little
Dr. Walter M. Little
Dr. Lynn Loach
Dr. E. Lorber
Dr. Donald Low
Dr. F.H. Lowy
Dr. John Lundon
Dr. Robert MacDonald
Dr. Ross C. MacKay
Dr. Robert MacKenzie
Dr. Susan MacKinnon
Dr. Stuart MacLeod
Dr. J.L. Madigan
Dr. Aaron Malkin
Dr. Dina Gordon Malkin
Dr. Constantine Mallin
Dr. Jaanus Marley
Dr. Joseph Marotta
Dr. A. Bruce Marshall
Dr. Ray Martin
Dr. B. Massouda
Dr. Nancy McKee
Dr. Rosemary Meier
Dr. Richard Miller
Dr. C.A.F. Moes
Dr. Kenneth Money
Dr. K. Moore
Dr. J.E. Morgan
Dr. Heather Morris
Dr. Rebeka Moscarello
Dr. David Murray
Dr. James F. Murray
Dr. James B.J. McKendry
Dr. Raymond M. McKeown
Dr. David McLeod
Dr. David McNeely
Dr. Salim Naqvi
Dr. William Nelson
Dr. Richard Ogilvie
Dr. H. Onyett
Dr. D. Oreopoulos
Dr. C.R. Pace-Asciak
Dr. Frederick Papsin
Dr. Robert Patten
Dr. George A. Patterson
Dr. Thomas Patterson
Dr. F.R. Pember
Dr. Gordon Pengelly
Dr. A.C. Percheson
Dr. Richard Perrin
Dr. W.J. Peters
Dr. Mel E. Petersiel
Dr. Charles Pollick
Dr. D.G. Pond
Dr. Peter Y. Poon
Dr. Anette Poon-Toye
Dr. Kathleen Pritchard
Dr. John Provan
Dr. Anita Rachlis
Dr. G. Ralph
Dr. James G. Rankin
Dr. William Reynolds
Dr. Dorianne E. Rheaume
Dr. Robert N. Richards
Dr. Robin Richards
Dr. Kenneth Robb
Dr. Alexander Roberts
Dr. Irving B. Rosen
Dr. Irving E. Rosen
Dr. Cheryl Rowe
Dr. Robert Ruderman
Dr. Donald Ryder
Dr. Fred Saibil
Dr. Isaac Sakinofsky
Dr. Robert Salter
Dr. Paul Sandor
Dr. Andrew Sass-Kortsak
Dr. Michael Schwartz
Dr. Arthur Scott
Dr. John Scott
Dr. Edward M. Sellers
Dr. Robert Sheppard
Dr. Jerry Shime
Dr. Jack Shuber
Dr. K.H. Shumak
Dr. Ruth Shykoff
Dr. Brian N. Silver
Dr. Daniel Silver
Dr. Bernard Silverman
Dr. W. John Simpson
Dr. J.Donald Smith
Dr. G.E.D. Snell
Dr. Susan Stafford
Dr. Donald A. Stewart
Dr. Stephen Stokl
Dr. Albert C. Strickler
Dr. Lorne Tarshis
Dr. Charles Tator
Dr. John R. Taylor
Dr. Ron Taylor
Toronto Bayview Clinic
Dr. A.A. Tountas
Dr. William Tucker
Dr. David Uden
Dr. Joan Vale
Dr. Mariam Vania
Dr. H. Terry Van Patten
Dr. Daniel G. Vaughan
Dr. Otto Veidlinger
Dr. Hillar Vellend
Dr. Robert Volpe
Dr. James P. Waddell
Dr. Paul G. Walfish
Dr. Gary D. Webb
Dr. R.K. Weber
Dr. Peter Webster
Dr. Richard D. Weisel
Dr. David Wesson
Dr. Catharine I. Whiteside
Dr. R.H. Wilkinson
Dr. Dan Wilmot
Dr. D.R. Wilson
Dr. Robert J. Wilson
Dr. & Mrs. Manley S. Wolochow
Dr. Colin Woolf
Dr. James Yao
Dr. John Zeldin
Dr. Walter Zingg

Pouring resources and knowledge into a dedicated fight against suffering.

Suffering costs nothing.

The pursuit of the perfect cure requires time, effort . . . and large sums of money.

At Ciba-Geigy, the question is not how much time or how much money, but how effective the end product is.

Which is why any breakthrough that results in the release of a new medicine is the culmination of long years of exhaustive and thorough research. It is, in fact, the creation of "new knowledge".

The initiation of such invaluable work would not be possible were it not for the direct participation of world-famous research institutions and organisations.

Significantly, the goal at Ciba-Geigy echoes that of mankind's – freedom from suffering.

PAAB
CCPP

CIBA—GEIGY

Creating new knowledge for a healthier world.